(54) Title: METHODS FOR DIAGNOSING AND TREATING HEART DISEASE

(57) Abstract: The invention provides methods of diagnosing heart disease, such as heart failure, screening methods for identifying compounds that can be used to treat or to prevent heart disease, and methods of using these compounds to treat or to prevent heart disease. The invention also provides animal model systems for carrying out the screening methods.

METHODS FOR DIAGNOSING AND TREATING HEART DISEASE

Field of the Invention

This invention relates to methods for diagnosing and treating heart disease.

Background of the Invention

Heart disease is a general term used to describe many different heart conditions. For example, coronary artery disease, which is the most common heart disease, is characterized by constriction or narrowing of the arteries supplying the heart with oxygen-rich blood, and can lead to myocardial infarction, which is the death of a portion of the heart muscle. Heart failure is a condition resulting from the inability of the heart to pump an adequate amount of blood through the body. Heart failure is not a sudden, abrupt stop of heart activity, but, rather, typically develops slowly over many years, as the heart gradually loses its ability to pump blood efficiently. Risk factors for heart failure include coronary artery disease, hypertension, valvular heart disease, cardiomyopathy, disease of the heart muscle, obesity, diabetes, and a family history of heart failure.

Summary of the Invention

The invention provides diagnostic, drug screening, and therapeutic methods based on the observation that mutation of the *titin* gene leads to a phenotype in zebrafish that is similar to mammalian heart failure.

In one aspect, the invention provides a method of determining whether a test subject (*e.g.*, a mammal, such as a human) has, or is at risk of developing, a titin-related disease or condition (*e.g.*, heart failure). This method involves analyzing a nucleic acid molecule of a sample from the

5   test subject to determine whether the test subject has a mutation (for example, a mutation in a cardiac-specific exon, such as the N2B exon; *e.g.*, the *pickwick* mutation; see below) in a *titin* gene. The presence of such a mutation is an indication that the test subject has, or is at risk of developing, a titin-related disease. This method can further involve using

10   nucleic acid molecule primers specific for the *titin* gene for nucleic acid molecule amplification of the *titin* gene by the polymerase chain reaction, or sequencing *titin* nucleic acid molecules from the test subject.

In another aspect, the invention provides a screening method for identifying a compound that can be used to treat or to prevent heart failure.

15   This method involves contacting an organism (*e.g.*, a zebrafish) having a *titin* mutation (for example, a mutation in a cardiac-specific exon, such as the N2B exon; *e.g.*, the *pickwick* mutation) and a phenotype characteristic of heart failure with the compound, and determining the effect of the compound on the phenotype. Detection of an improvement in the

20   phenotype indicates the identification of a compound that can be used to treat or to prevent heart failure.

In another aspect, the invention provides a method of treating or preventing heart disease, such as heart failure, in a patient. This method involves administering to the patient a compound identified using the

25   screening method described above. A patient treated using this method can have a mutation in the *titin* gene.

In a further aspect, the invention provides a non-human animal (*e.g.*, a zebrafish or a mouse) that has a mutation in a *titin* gene. The

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mutation can be, for example, in a cardiac-specific exon of the *titin* gene, such as the N2B exon, and can result in production of a truncated titin product, for example, by the introduction of a stop codon.

By "polypeptide" or "polypeptide fragment" is meant a chain of

5   two or more amino acids, regardless of any post-translational modification (*e.g.*, glycosylation or phosphorylation), constituting all or part of a naturally or non-naturally occurring polypeptide. By "post-translational modification" is meant any change to a polypeptide or polypeptide fragment during or after synthesis. Post-translational modifications can be

10 produced naturally (such as during synthesis within a cell) or generated artificially (such as by recombinant or chemical means). A "protein" can be made up of one or more polypeptides.

By "titin," "titin protein," or "titin polypeptide" is meant a polypeptide that has at least 45%, preferably at least 60%, more preferably

15 at least 75%, and most preferably at least 90% amino acid sequence identity to the sequence of the human (see below) or the zebrafish titin polypeptides. Polypeptide products from splice variants of *titin* gene sequences and *titin* genes containing mutations are also included in this definition. A titin polypeptide as defined herein plays a role in heart

20 development, modeling, structure, and contractility. It can be used as a marker of heart disease, such as heart failure.

By a "*titin* nucleic acid molecule" is meant a nucleic acid molecule, such as a genomic DNA, cDNA, or RNA (*e.g.*, mRNA) molecule, that encodes titin, a titin protein, a titin polypeptide, or a portion thereof, as

25 defined above.

The term "identity" is used herein to describe the relationship of the sequence of a particular nucleic acid molecule or polypeptide to the sequence of a reference molecule of the same type. For example, if a

polypeptide or nucleic acid molecule has the same amino acid or nucleotide residue at a given position, compared to a reference molecule to which it is aligned, there is said to be "identity" at that position. The level of sequence identity of a nucleic acid molecule or a polypeptide to a

5 reference molecule is typically measured using sequence analysis software with the default parameters specified therein, such as the introduction of gaps to achieve an optimal alignment (e.g., Sequence Analysis Software Package of the Genetics Computer Group, University of Wisconsin Biotechnology Center, 1710 University Avenue, Madison, WI 53705,

10 BLAST, or PILEUP/PRETTYBOX programs). These software programs match identical or similar sequences by assigning degrees of identity to various substitutions, deletions, or other modifications. Conservative substitutions typically include substitutions within the following groups: glycine, alanine, valine, isoleucine, and leucine; aspartic acid, glutamic

15 acid, asparagine, and glutamine; serine and threonine; lysine and arginine; and phenylalanine and tyrosine.

A nucleic acid molecule or polypeptide is said to be "substantially identical" to a reference molecule if it exhibits, over its entire length, at least 51%, preferably at least 55%, 60%, or 65%, and most preferably

20 75%, 85%, 90%, or 95% identity to the sequence of the reference molecule. For polypeptides, the length of comparison sequences is at least 16 amino acids, preferably at least 20 amino acids, more preferably at least 25 amino acids, and most preferably at least 35 amino acids. For nucleic acid molecules, the length of comparison sequences is at least 50

25 nucleotides, preferably at least 60 nucleotides, more preferably at least 75 nucleotides, and most preferably at least 110 nucleotides.

A *titin* nucleic acid molecule or titin polypeptide is "analyzed" or subject to "analysis" if a test procedure is carried out on it that allows the

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determination of its biological activity or whether it is wild type or mutated. For example, one can analyze the *titin* genes of an animal (*e.g.*, a human or a zebrafish) by amplifying genomic DNA of the animal using the polymerase chain reaction, and then determining whether the amplified

5 DNA contains a mutation, for example, the *pickwick* mutation, by, *e.g.*, nucleotide sequence or restriction fragment analysis.

By "probe" or "primer" is meant a single-stranded DNA or RNA molecule of defined sequence that can base pair to a second DNA or RNA molecule that contains a complementary sequence ("target"). The stability

10 of the resulting hybrid depends upon the extent of the base pairing that occurs. This stability is affected by parameters such as the degree of complementarity between the probe and target molecule, and the degree of stringency of the hybridization conditions. The degree of hybridization stringency is affected by parameters such as the temperature, salt

15 concentration, and concentration of organic molecules, such as formamide, and is determined by methods that are well known to those skilled in the art. Probes or primers specific for *titin* nucleic acid molecules, preferably, have greater than 45% sequence identity, more preferably at least 55-75% sequence identity, still more preferably at least 75-85% sequence identity,

20 yet more preferably at least 85-99% sequence identity, and most preferably 100% sequence identity to the sequences of human (see below) or zebrafish *titin*.

Probes can be detectably-labeled, either radioactively or non-radioactively, by methods that are well-known to those skilled in the art.

25 Probes can be used for methods involving nucleic acid hybridization, such as nucleic acid sequencing, nucleic acid amplification by the polymerase chain reaction, single stranded conformational polymorphism (SSCP) analysis, restriction fragment polymorphism (RFLP) analysis, Southern

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hybridization, northern hybridization, *in situ* hybridization, electrophoretic mobility shift assay (EMSA), and other methods that are well known to those skilled in the art.

A molecule, *e.g.*, an oligonucleotide probe or primer, a gene or fragment thereof, a cDNA molecule, a polypeptide, or an antibody, can be said to be "detectably-labeled" if it is marked in such a way that its presence can be directly identified in a sample. Methods for detectably-labeling molecules are well known in the art and include, without limitation, radioactive labeling (*e.g.*, with an isotope, such as ^{32}P or ^{35}S) and nonradioactive labeling (*e.g.*, with a fluorescent label, such as fluorescein).

By a "substantially pure polypeptide" is meant a polypeptide (or a fragment thereof) that has been separated from proteins and organic molecules that naturally accompany it. Typically, a polypeptide is substantially pure when it is at least 60%, by weight, free from the proteins and naturally-occurring organic molecules with which it is naturally associated. Preferably, the polypeptide is a titin polypeptide that is at least 75%, more preferably at least 90%, and most preferably at least 99%, by weight, pure. A substantially pure titin polypeptide can be obtained, for example, by extraction from a natural source (*e.g.*, isolated heart tissue), by expression of a recombinant nucleic acid molecule encoding a titin polypeptide, or by chemical synthesis. Purity can be measured by any appropriate method, *e.g.*, by column chromatography, polyacrylamide gel electrophoresis, or HPLC analysis.

A polypeptide is substantially free of naturally associated components when it is separated from those proteins and organic molecules that accompany it in its natural state. Thus, a protein that is chemically synthesized or produced in a cellular system different from the

cell in which it is naturally produced is substantially free from its naturally associated components. Accordingly, substantially pure polypeptides not only include those derived from eukaryotic organisms, but also those synthesized in *E. coli* or other prokaryotes.

5   An antibody is said to "specifically bind" to a polypeptide if it recognizes and binds to the polypeptide (*e.g.*, a titin polypeptide), but does not substantially recognize and bind to other molecules (*e.g.*, non-titin related polypeptides) in a sample, *e.g.*, a biological sample that naturally includes the polypeptide.

10   By "high stringency conditions" is meant conditions that allow hybridization comparable with the hybridization that occurs using a DNA probe of at least 500 nucleotides in length, in a buffer containing 0.5 M NaHPO$_4$, pH 7.2, 7% SDS, 1 mM EDTA, and 1% BSA (fraction V), at a temperature of 65°C, or a buffer containing 48% formamide, 4.8 x SSC,

15 0.2 M Tris-Cl, pH 7.6, 1 x Denhardt's solution, 10% dextran sulfate, and 0.1% SDS, at a temperature of 42°C. (These are typical conditions for high stringency northern or Southern hybridizations.) High stringency hybridization is also relied upon for the success of numerous techniques routinely performed by molecular biologists, such as high stringency PCR,

20 DNA sequencing, single strand conformational polymorphism analysis, and *in situ* hybridization. In contrast to northern and Southern hybridizations, these techniques are usually performed with relatively short probes (*e.g.*, usually 16 nucleotides or longer for PCR or sequencing and 40 nucleotides or longer for *in situ* hybridization). The high

25 stringency conditions used in these techniques are well known to those skilled in the art of molecular biology, and examples of them can be

found, for example, in Ausubel *et al.*, *Current Protocols in Molecular Biology*, John Wiley & Sons, New York, NY, 1998, which is hereby incorporated by reference.

By "sample" is meant a tissue biopsy, amniotic fluid, cell, blood,
5　serum, urine, stool, or other specimen obtained from a patient or test subject. The sample can be analyzed to detect a mutation in a *titin* gene, or expression levels of a *titin* gene, by methods that are known in the art. For example, methods such as sequencing, single-strand conformational polymorphism (SSCP) analysis, or restriction fragment length
10　polymorphism (RFLP) analysis of PCR products derived from a patient sample can be used to detect a mutation in a *titin* gene; ELISA can be used to measure levels of titin polypeptide; and PCR can be used to measure the level of a *titin* nucleic acid molecule.

By "titin-related disease" or "titin-related condition" is meant a
15　disease or condition that results from inappropriately high or low expression of a *titin* gene, or a mutation in a *titin* gene that alters the biological activity of a *titin* nucleic acid molecule or polypeptide. Titin-related diseases and conditions can arise in any tissue in which titin is expressed during prenatal or post-natal life. Titin-related diseases and
20　conditions can include heart diseases, such as heart failure. Specific examples of different types of heart failure are provided below.

The invention provides several advantages. For example, using the diagnostic methods of the invention, it is possible to detect an increased likelihood of heart disease, such as heart failure, in a patient, so that
25　appropriate intervention can be instituted before any symptoms occur. This may be useful, for example, with patients in high-risk groups for heart failure (see above). Also, the diagnostic methods of the invention facilitate determination of the etiology of an existing heart condition, such

as heart failure, in a patient, so that an appropriate approach to treatment can be selected. In addition, the screening methods of the invention can be used to identify compounds that can be used to treat or to prevent heart conditions, such as heart failure.

5   Other features and advantages of the invention will be apparent from the following detailed description and the claims.

Brief Description of the Drawing

Fig. 1 is a schematic representation of the domain structure of the human titin filament. The nucleotide and amino acid sequences of human

10 titin are provided in SEQ ID NOs:1 and 2, respectively. The modular architecture of cardiac titin as predicted by its full-length cDNA is shown.

A total of 244 copies of 100 residue repeats, as indicated by vertical rectangles, are contained in the molecule. One hundred and twelve of these belong to the Ig domain, and 132 belong to the FN3 superfamily.

15 The titin kinase domain, as well as the PEVK element N2-B 163-residue variant are also shown. Within the A-band , the D-zone contains six tandem repeats of the seven domains shown (A1 through A42), and the C-zone contains 11 tandem repeats of the 11 domains shown (A43 through A163). The positions of the tandemly repeated RMSP and VKSP motifs

20 in the Z-disc and M-line region are also shown

Detailed Description

The invention provides methods of diagnosing heart disease, screening methods for identifying compounds that can be used to treat or to prevent heart disease, and methods of treating or preventing heart

disease using these compounds. The invention also provides animal model systems that can be used in the screening methods of the invention.

In particular, we have discovered that a mutation (the *pickwick* mutation) in the *titin* gene is associated with heart disease, such as heart

5 failure. Titin, which is also known as "connectin," is the largest known single-chain protein, having a molecular weight of about 3,000 kDa. Titin is a structural protein, and plays a central role in the assembly and elasticity of vertebrate skeletal and cardiac muscle. Thus, the diagnostic methods of the invention involve detection of mutations in the *titin* gene,

10 while the compound identification methods of the invention involve screening for compounds that affect the phenotype of *titin* mutants or other models of heart disease, such as heart failure. Compounds identified in this manner can be used in methods to treat or to prevent heart disease (*e.g.*, heart failure). The diagnostic, screening, and therapeutic methods of

15 the invention, as well as the animal model systems of the invention, are described further, as follows.

Diagnostic Methods

Titin nucleic acid molecules, polypeptides, and antibodies can be used in methods to diagnose or to monitor diseases and conditions

20 involving mutations in, or inappropriate expression of, *titin* genes. As discussed further below, the *pickwick* mutation in zebrafish, which is present in the *titin* gene, is characterized by a phenotype that is similar to that of heart failure in humans. Thus, detection of abnormalities in *titin* genes or their expression can be used in methods to diagnose, or to

25 monitor treatment or development of, human heart disease, such as heart failure. For use as references, the human cardiac *titin* cDNA sequence can be found at:

http://www.embl-heidelberg.de/ExternalInfo/Titin/cardiacseq.html (SEQ
ID NO:1), while the corresponding protein sequence can be found at:
http://www.embl-heidelberg.de/ExternalInfo/Titin/cardiacpep.html (SEQ
ID NO:2).

5   As noted above, the diagnostic methods of the invention can be
used, for example, with patients that have heart failure, in an effort to
determine its etiology and, thus, to facilitate selection of an appropriate
course of treatment. The diagnostic methods can also be used with
patients that have not yet developed heart failure, but who are at risk of
10   developing such a disease, or with patients that are at an early stage of
developing such a disease. Also, the diagnostic methods of the invention
can be used in prenatal genetic screening, for example, to identify parents
who may be carriers of a recessive *titin* mutation.

Examples of heart failure that can be diagnosed (and treated) using
15   the methods of the invention include congestive heart failure, which is
characterized by fluid in the lungs or body, resulting from failure of the
heart in acting as a pump; right sided heart failure (right ventricular),
which is characterized by failure of the pumping action of the right
ventricle, resulting in swelling of the body, especially the legs and
20   abdomen; left sided heart failure (left ventricular), which is caused by
failure of the pumping action of the left side of the heart, resulting in
congestion of the lungs; forward heart failure, which is characterized by
the inability of the heart to pump blood forward at a sufficient rate to meet
the oxygen needs of the body at rest or during exercise; backward heart
25   failure, which is characterized by the ability of the heart to meet the needs
of the body only if heart filling pressures are abnormally high; low-output,

which is characterized by failure to maintain blood output; and
high-output, which is characterized by heart failure symptoms, even when
cardiac output is high.

    Titin may also play a role in cardiovascular diseases other than
5 heart failure, such as coronary artery disease or conditions associated with
valve formation defects, and, thus, detection of abnormalities in *titin* genes
or their expression can be used in methods to diagnose and monitor these
conditions as well. The methods of the invention can be used to diagnose
(or to treat) the disorders described herein in any mammal, for example,
10 humans, domestic pets, or livestock.

    Titin abnormalities that can be detected using the diagnostic
methods of the invention include those characterized by, for example, (i)
abnormal titin polypeptides, (ii) *titin* genes containing mutations that result
in the production of such polypeptides, and (iii) *titin* mutations that result
15 in production of abnormal amounts of titin. Detection of such
abnormalities, thus, can be used in methods to diagnose human heart
disease, such as heart failure. Exemplary of the *titin* mutations that can be
detected using the methods of the invention is the *pickwick* mutation (see
below).

20   Detection of *titin* mutations can be carried out using any diagnostic
technique. For example, a biological sample obtained from a patient can
be analyzed for one or more mutations in *titin* nucleic acid molecules (*e.g.*,
the *pickwick* mutation) using a mismatch detection approach. Generally,
this approach involves polymerase chain reaction (PCR) amplification of
25 nucleic acid molecules from a patient sample, followed by identification of
a mutation (*i.e.*, a mismatch) by detection of altered hybridization, aberrant
electrophoretic gel migration, binding, or cleavage mediated by mismatch
binding proteins, or by direct nucleic acid molecule sequencing. Any of

these techniques can be used to facilitate detection of mutant *titin* genes, and each is well known in the art. Examples of these techniques are described by Orita *et al.* (Proc. Natl. Acad. Sci. U.S.A. 86:2766-2770, 1989) and Sheffield *et al.* (Proc. Natl. Acad. Sci. U.S.A. 86:232-236,

5 1989).

Mutation detection assays also provide an opportunity to diagnose a titin-mediated predisposition to heart disease before the onset of symptoms. For example, a patient heterozygous for a *titin* mutation that suppresses normal titin biological activity or expression may show no

10 clinical symptoms of a titin-related disease, and yet possess a higher than normal probability of developing heart disease, such as heart failure. Given such a diagnosis, a patient can take precautions to minimize exposure to adverse environmental factors, and can carefully monitor their medical condition, for example, through frequent physical examinations.

15 As mentioned above, this type of diagnostic approach can also be used to detect *titin* mutations in prenatal screens.

The *titin* diagnostic assays described above can be carried out using any biological sample (for example, a muscle tissue sample) in which titin is normally expressed. Because of the limited number of tissues in which

20 titin is expressed, as well as the relative difficulties involved in obtaining samples of these tissues, it may be preferable to detect mutant *titin* genes in another, more easily obtained sample type, such as blood or amniotic fluid samples using, for example, mismatch detection techniques. Preferably, the DNA in such a sample is subjected to PCR amplification

25 prior to analysis.

Levels of titin expression in a patient sample can be determined by using any of a number of standard techniques that are well known in the art. For example, titin expression in a biological sample (*e.g.*, a blood or

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tissue sample, or amniotic fluid) from a patient can be monitored by
standard northern blot analysis or by quantitative PCR (see, *e.g.*, Ausubel
et al., *supra*; *PCR Technology: Principles and Applications for DNA
Amplification*, H.A. Ehrlich, Ed., Stockton Press, NY; Yap *et al.*, Nucl.
5   Acids. Res. 19:4294, 1991).

In yet another diagnostic approach of the invention, an
immunoassay is used to detect or to monitor titin protein levels in a
biological sample. Titin-specific polyclonal or monoclonal antibodies can
be used in any standard immunoassay format (*e.g.*, ELISA, Western blot,
10   or RIA; see, *e.g.*, Ausubel *et al.*, *supra*) to measure titin polypeptide levels.
These levels are compared to wild-type titin levels. For example, a
decrease in titin production may be indicative of a condition or a
predisposition to a condition involving insufficient titin biological activity.

Immunohistochemical techniques can also be utilized for titin
15   detection. For example, a tissue sample can be obtained from a patient,
sectioned, and stained for the presence of titin using an anti-titin antibody
and any standard detection system (*e.g.*, one that includes a secondary
antibody conjugated to horseradish peroxidase). General guidance
regarding such techniques can be found in, *e.g.*, Bancroft *et al.*, *Theory*
20   *and Practice of Histological Techniques*, Churchill Livingstone, 1982, and
in Ausubel *et al.*, *supra*.

Identification of Molecules That Can Be Used to Treat or to Prevent Heart
Failure

Identification of a mutation in *titin* as resulting in a phenotype that
25   is related to heart failure facilitates the identification of molecules (*e.g.*,
small organic molecules, peptides, or nucleic acid molecules) that can be

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used to treat or to prevent heart failure. The effects of candidate compounds on heart failure can be investigated using, for example, the zebrafish system. The zebrafish, *Danio rerio*, is a convenient organism to use in genetic analysis of vascular development. In addition to its short

5 generation time and fecundity, it has an accessible and transparent embryo, allowing direct observation of blood vessel function from the earliest stages. As discussed further below, zebrafish and other animals having mutations in the *titin* gene, which can be used in these methods, are also included in the invention.

10   In one example of the screening methods of the invention, a zebrafish having a mutation in the *titin* gene (*e.g.*, a zebrafish having the *pickwick* mutation; see below) is contacted with a candidate compound, and the effect of the compound on the development of a heart abnormality that is characteristic of heart failure, or on the status of such an existing

15 heart abnormality, is monitored, relative to an untreated, identically mutant control. As discussed further below, zebrafish having the *pickwick* mutation are characterized by, for example, reduction of peak systolic pressures, stretched and thin myocardium, excess cardiac jelly, absent A-V cushions, and an obstructed ventricular outflow tract. Thus, these

20 characteristics (in addition to other characteristics of heart failure) can be monitored using the screening methods of the invention.

        After a compound has been shown to have a desired effect in the zebrafish system, it can be tested in other models of heart disease, for example, in mice or other animals having a mutation in the *titin* gene.

25 Alternatively, testing in such animal model systems can be carried out in the absence of zebrafish testing.

        Candidate compounds can be purified (or substantially purified) molecules or can be one component of a mixture of compounds (*e.g.*, an

extract or supernatant obtained from cells; Ausubel *et al.*, *supra*). In a mixed compound assay, the effect on a phenotype of heart failure is tested against progressively smaller subsets of the candidate compound pool (*e.g.*, produced by standard purification techniques, *e.g.*, HPLC or FPLC)

5 until a single compound or minimal compound mixture is demonstrated to have the desired effect.

Test compounds that can be screened in the methods described above can be chemicals that are naturally occurring or artificially derived. Such compounds can include, for example, polypeptides, synthesized

10 organic molecules, naturally occurring organic molecules, nucleic acid molecules, and components thereof. Candidate compound can be found, for example, in a cell extract, mammalian serum, or growth medium in which mammalian cells have been cultured.

In general, novel drugs for prevention or treatment of mutant titin-

15 related heart diseases can be identified from large libraries of both natural products, synthetic (or semi-synthetic) extracts, and chemical libraries using methods that are well known in the art. Those skilled in the field of drug discovery and development will understand that the precise source of test extracts or compounds is not critical to the screening methods of the

20 invention. Accordingly, virtually any number of chemical extracts or compounds can be screened using these methods. Examples of such extracts or compounds include, but are not limited to, plant-, fungal-, prokaryotic-, or animal-based extracts, fermentation broths, and synthetic compounds, as well as modifications of existing compounds.

25 Numerous methods are also available for generating random or directed synthesis (*e.g.*, semi-synthesis or total synthesis) of any number of chemical compounds, including, but not limited to, saccharide-, lipid-, peptide-, and nucleic acid molecule-based compounds. Synthetic

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compound libraries are commercially available from Brandon Associates (Merrimack, NH) and Aldrich Chemical (Milwaukee, WI). Alternatively, libraries of natural compounds in the form of bacterial, fungal, plant, and animal extracts are commercially available from a number of sources,

5   including Biotics (Sussex, UK), Xenova (Slough, UK), Harbor Branch Oceanographic Institute (Ft. Pierce, FL), and PharmaMar, U.S.A. (Cambridge, MA). In addition, natural and synthetically produced libraries can be produced, if desired, according to methods known in the art, *e.g.*, by standard extraction and fractionation. Furthermore, if desired,

10   any library or compound can be readily modified using standard chemical, physical, or biochemical methods.

In addition, those skilled in the art of drug discovery and development readily understand that methods for dereplication (*e.g.*, taxonomic dereplication, biological dereplication, and chemical

15   dereplication, or any combination thereof) or the elimination of replicates or repeats of materials already known for their therapeutic activities for heart failure can be employed whenever possible.

When a crude extract is found to have an effect on the development or persistence of heart failure, further fractionation of the positive lead

20   extract can be carried out to isolate chemical constituents responsible for the observed effect. Thus, the goal of the extraction, fractionation, and purification process is the careful characterization and identification of a chemical entity within the crude extract having a desired activity. The same assays described herein for the detection of activities in mixtures of

25   compounds can be used to purify the active component and to test derivatives of these compounds. Methods of fractionation and purification of such heterogeneous extracts are well known in the art. If desired,

compounds shown to be useful agents for treatment can be chemically modified according to methods known in the art.

Treatment or Prevention of Heart Failure

Compounds identified using the screening methods described above

5 can be used to treat patients that have or are at risk of developing heart disease, such as heart failure. Such treatment may be required only for a short period of time, or may, in some form, be required throughout a patient's lifetime. Any continued need for treatment, however, can be determined using, for example, the diagnostic methods described above.

10 In considering various therapies, it is understood that such therapies are, preferably, targeted to the affected or potentially affected organ, that is, the heart.

Treatment or prevention of diseases resulting from a mutated *titin* gene can be accomplished, for example, by modulating the function of a

15 mutant titin protein, delivering normal titin protein to the appropriate cells, altering the levels of normal or mutant titin protein, replacing a mutant *titin* gene with a normal *titin* gene or, administering a normal *titin* gene. It is also possible to correct a *titin* defect by modifying the physiological pathway (*e.g.*, a signal transduction pathway) in which the titin protein

20 participates.

In a patient diagnosed as heterozygous for a *titin* mutation, or as susceptible to *titin* mutations or aberrant titin expression (even if those mutations or expression patterns do not yet result in alterations in titin expression or biological activity), any of the above-described therapies can

25 be administered before the occurrence of the disease phenotype. In particular, compounds shown to modulate titin expression or to have an

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effect on the phenotype of *titin* mutants can be administered to patients diagnosed with potential or actual heart disease by any standard dosage and route of administration.

Any appropriate route of administration can be employed to

5 administer a compound found to be effective in treating or preventing heart failure, according to the invention. For example, administration can be parenteral, intravenous, intra-arterial, subcutaneous, intramuscular, intraventricular, intracapsular, intraspinal, intracisternal, intraperitoneal, intranasal, aerosol, or oral. However, as noted above, preferably, the

10 administration is local to the afflicted tissue, that is, the heart. Therapeutic formulations can be in the form of liquid solutions or suspensions; for oral administration, formulations can be in the form of tablets or capsules; and for intranasal formulations, in the form of powders, nasal drops, or aerosols.

15   A therapeutic compound of the invention can be administered within a pharmaceutically acceptable diluent, carrier, or excipient, in unit dosage form. Administration can begin before or after the patient is symptomatic. Methods that are well known in the art for making formulations are found, for example, in *Remington's Pharmaceutical*

20 *Sciences*, (18th edition), ed. A. Gennaro, 1990, Mack Publishing Company, Easton, PA. Formulations for parenteral administration can, for example, contain excipients; sterile water; or saline; polyalkylene glycols, such as polyethylene glycol; oils of vegetable origin; or hydrogenated napthalenes. Biocompatible, biodegradable lactide polymer, lactide/glycolide

25 copolymer, or polyoxyethylene-polyoxypropylene copolymers can be used to control the release of the compounds. Other potentially useful parenteral delivery systems for compounds identified using the methods of the invention include ethylene-vinyl acetate copolymer particles, osmotic

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pumps, implantable infusion systems, and liposomes. Formulations for inhalation can contain excipients, for example, lactose, or can be aqueous solutions containing, for example, polyoxyethylene-9-lauryl ether, glycocholate, and deoxycholate, or can be oily solutions for administration

5 in the form of nasal drops, or as a gel.

Titin nucleic acid molecules and polypeptides can also be used in tissue engineering, for example, in the manufacture of artificial or partially artificial hearts. As mentioned above, titin plays a role in cardiovascular elasticity, integrity, and contractility. Thus, a *titin* nucleic acid molecule

10 or polypeptide, as described above, can be used to impart such characteristics on an artificial or partially artificial heart.

Animal Model Systems

The invention also provides animal model systems for use in carrying out the screening methods described above. Examples of these

15 model systems include zebrafish and other animals, such as mice, that have mutations in a *titin* gene. For example, a zebrafish model that can be used in the invention can include a mutation that results in a lack of titin production or production of a truncated (*e.g.*, by introduction of a stop codon) or otherwise altered titin gene product. The mutation can, for

20 example, result in the presence of a stop codon in a cardiac-specific exon, such as the N2B exon (*e.g.*, in the IS3 region; see below). The mutation can be in a region encoding the I band, resulting in the production of a protein in which the I band is truncated and the A band and M line are absent, or can be in a region encoding another portion of the molecule,

25 such as the A band or M line region. As a specific example, a zebrafish having the *pickwick* mutation can be used.

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Experimental Results

     During a large-scale mutagenesis screening of the zebrafish genome, a group of mutations were identified that affect cardiac contractility. One of these mutations, called *pickwick* (*pik*), dramatically

5 reduces the function of both chambers, causing a recessive, lethal form of heart failure in the zebrafish embryo.

     Direct *in vivo* recording of ventricular pressures by the null balance feedback system shows that *pickwick* causes a 5.8 fold reduction of peak systolic pressures, compared to age-matched controls (0.084+/- 0.008 vs.

10 0.49+/- 0.06 mm Hg). Morphological analysis of *pickwick* revealed a stretched and thin myocardium, excess cardiac jelly, absent A-V cushions, and an obstructed ventricular outflow tract. Extensive ultrastructural defects were found by transmission electron microscopy, affecting the assembly of Z-discs and the organization of myofilaments. Reciprocal

15 blastomere transplants identified *pickwick* as a cell autonomously acting mutation of the myoblast lineage.

     A positional cloning approach was adopted for gene identification. The *pickwick* mutation has been assigned to a small chromosomal interval, which is covered by BAC clones. The *titin* gene spans this interval, and

20 thus the *pickwick* phenotype is due to a mutation in the *titin* gene. In particular, the *pickwick* gene was mapped to linkage group (LG) 9 by bulk segregant analysis using the *pikm242* allele, which is one of five cardiac specific alleles (*pikm242, pikm171, pikm740, pikm186, pikmnm2*). A panel of Z-markers in the linkage group was tested for simple sequence

25 length polymorphisms (SSLPs) using 931 homozygous mutant embryos. Markers Z8363 and Z26463 were shown to flank the *pickwick* locus, defining a 1.2 cM interval containing the gene. It is estimated that 1 cM corresponds to 500-600 kb DNA in the zebrafish genome (Postlethwait *et*

al., Science 264:699-703, 1994). We thus initiated chromosomal walking from the Z8363 marker, which is 0.7 cM from the mutation (12 recombinants out of 1750 meioses).

A positive YAC clone (YAC5) was identified that had a T7 end that
5   is highly homologous to human *titin* coding sequences. As the *titin* genomic region was estimated to be over 300 kb in humans, we decided to identify BAC clones based on sequence information of the zebrafish *titin* EST clones. A physical contig was constructed based on these sequences, which covers the whole *titin* genomic area. Single stranded
10 conformational polymorphisms (SSCPs) were developed from the ends and internal sequences of these clones were used for fine recombinational mapping. One SSCP marker inside the *titin* genomic area (B9F2) picked up one recombinant from the Z26463 side. The other four SSCP markers inside the *titin* genomic area (B4SP1, B2T7, B7SP, and B6SP) picked up
15 zero recombinants out of 1750 meioses. These genetic data indicated that the *pickwick* locus is very close to or within the *titin* genomic region.

As the *titin* cDNA alone is around 82 kb, rescuing the phenotype by RNA injection could prove to be quite difficult. However, we found evidence that the *pickwick* locus is within the *titin* gene by identification of
20 point mutations in one of the *pickwick* alleles. As most of the alleles of *pickwick* have a cardiac-specific phenotype, we presumed that the point mutation is located in a cardiac-specific exon. We focused on the N2B domain in the I-band of titin, as all of the cardiac isoforms are N2B domain based. The zebrafish N2B domain was cloned by RT-PCR. It is a
25 4.3 kb cDNA encoding infrastructures similar to those in humans and mice, and contains 4 IG repeats and three unique sequences, including longer IS3 and shorter IS1.

N2B domains from *pickwick* mutant embryos were then cloned. RNA mismatch analysis was performed to identify the location of the point mutation. One mismatch between the PCR products from *pikm171* and *pikm242* was identified. Sequencing of the PCR product resulted in

5   the identification of a T-> G transition in the *pikm171* allele. This mutation resulted in a change of leucine in the IS3 fragment of N2B domain (N2B-IS3) into a stop codon. The mutation was confirmed in all of the seven homozygous *pikm171* mutant embryos, but none of the four *pikm242* homozygous embryos. A truncated version of titin is predicted to

10   be in the *pikm171* mutant, only as a cardiac specific isoform. It should contain the Z-disc and part of the I-band and be sized around 4,000 amino acids, based on comparison to the homologous human titin sequence, which has a full length of 27,000 amino acids. The identification of a non-sense mutation in the cardiac specific N2B domain in *pikm171* allele

15   confirmed the hypothesis that *titin* is the *pickwick* gene.

Titin was expressed in the zebrafish embryo during the period when the *pickwick* phenotype was first detected. Whole mount *in situ* hybridization analysis indicated that *titin* was expressed strongly in both the heart and the somites at 24 hpf. *Titin* mRNA expression in the heart is

20   normal in *pikm171*. We confirmed the notion that N2B is a cardiac-specific exon in zebrafish by labeling a probe in the IS3 domain for the whole mount *in situ* hybridization.

The identification of a point mutation in the N2B domain thus establishes *pickwick* as the first *in vivo* vertebrate system to study the

25   functions of titin in the heart. If titin functions as a spring, as proposed, it is expected that the contraction will be much weaker. This is exactly what we observed in pickwick mutant embryos. If titin functions as a template during the sarcomere assembly, a "silent heart" phenotype would be

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expected in titin null mutation. According to the current model of the myofibrillogenesis (Dabiri *et al.*, Proc. Natl. Acad. Sci. U.S.A. 94:9493-9498, 1997), the thick element and/or the sarcomere could not assemble into a beating machine. In contrast, the hearts in the homozygous *pikm171*

5 mutant embryos and all of the other *pickwick* alleles still beat, despite being weaker.

The mutation in *pikm171* predicts a truncated protein in which most of the elastic I-band is deleted and the C-terminal A-band and M-line regions eliminated. It thus could be considered as a null mutation in terms

10 of function as a spring and a potential dominant negative mutation in terms of its function as a template for sarcomere assembly (Turnacioglu *et al.*, Mol. Biol. Cell 8:705-717, 1997). The observation of the weak beating in the *pickwick* mutant embryos suggested the existence of primary contractile machinery without titin. Indeed, thick and thin elements can be

15 detected in the ventricular myocardium cells. They have the capacity to assemble into a functional beating structure in the absence of titin.

We thus have carried out a detailed physiological and morphological analysis of *pickwick*, a zebrafish heart function mutation that reduces the contractility of both chambers. Several pieces of evidence

20 pointed out that *titin* is the *pickwick* gene. Genetic analysis linked the *pickwick* locus closely to the *titin* genomic area. The identification of the *pikmVO62H*, a *pickwick* allele that has an additional somite phenotype, can be explained by the titin hypothesis. The point mutation is expected to be in the common exons that are shared between the cardiac and somatic

25 isoforms of titin. Evidence confirming this hypothesis came from the identification of a point mutation in the cardiac specific N2B domain of titin in one of the *pickwick* alleles, *pikm171*. We went on to show that sarcomere structure is disrupted in the myocardium cells of *pikm171*, but

not the somatic muscle cells. The expression pattern of titin is consistent with this phenotype. Strong expression in both cardiac and skeletal muscles was detected at the onset of the *pickwick* phenotype.

Thus, our observation in zebrafish is in consistent with the notion
5 that titin functions as a spring during the muscle contraction. As titin is a sarcomere structure protein, it is conceivable that myocardium is affected cell-autonomously in *pickwick* mutant embryos. The thin and stretched morphology could be due to the mechanic tension generated from the failure to form higher-order sarcomere structure and the loss of spring.
10 The mechanic tension may also be the reason for the separation between the myocardium cells and endocardium cells, generating the excess cardiac jelly. However, there is a possibility that the differentiation program of the myocardium was affected in the *titin* mutation. The valve formation phenotype in *pickwick* mutant embryos could be a secondary defect. It has
15 been suggested that the process of endothelial invasion during valve formation is under control of a localized myocardial signal. (For a review, see Fishman *et al.*, Development 124:2099-2117, 1997.) The physical distance between myocardium and endocardium and/or the stalked differential program in the myocardium could be the reason that prevents a
20 normal cushion formation.

Material and Methods
Zebrafish strains and maintenance
Zebrafish were maintained and staged as described. *pikm242*, *pikm171*, *pikm740*, *pikm186* were generated in a screen on the AB
25 background (Stainier *et al.*, Development 123:285-292, 1996). *pikmVO62H* and *pikmnml2* were generated in a screen on the TL background. Mapping strains were constructed by crossing *pikm242* into

25

india strain. *pikm171* embryos used in expression analysis and EM were obtained from pair wise matings of *pikm171*/TL heterozygotes.

In situ hybridization

Whole mount *in situ* hybridization was performed as described

5   (Thisse *et·al.*, Development 119:1203-1215, 1993). T5 probe was generated by digestion of the EST clone AI629069 (Research Genetics). The N2B and N2A probe were generated through PCR with a tagged T7 promoter. The primer pairs are:

P238F: 5'-AGGGACACTCAGAGACCATAG (SEQ ID NO:3); and

10 P3785RT: 5'-

TAATACGACTCACTATAGGGGTCTGAGGATACTCGCCTTC (SEQ ID NO:4).

Mapping of *pickwick*

Linkage was established using DNA from 16 homozygous

15 mutations and 16 heterozygous or wild type pick *pikm242*/indian embryos in bulk segregation analysis (Michelmore *et al.*, Proc. Natl. Acad. Sci. U.S.A. 88:9828-9832, 1991). Z-markers (simple sequence length polymorphisms, SSLP) were developed in this lab (Knapik *et al.*, Nat. Genet. 18:338-343, 1998; Shimoda *et al.*, Genomics 58:219-232, 1999).

20 Genotyping products were resolved in 6% PAGE gels.

Chromosomal walking

YAC and BAC clones were screened by PCR as pools of clones (Research Genetics) according to the manufacturer's instruction. YAC ends were cloned by plasmid rescue (Zhong *et al.*, Genomics 48:136-138,

25 1998). Chimeric ends were determined by the RH panel (Geisler *et al.*,

Nat. Genet. 23:86-89, 1999). BAC DNA was extracted using the QIAgene

kit and the end sequences were determined by direct sequencing. BLAST-

X was performed to search for homologous sequence in Genebank. EST

clones were generated by Washington University zebrafish EST project

5   and obtained from Research Genetics. Oligonucleotides derived from the

end sequences of YAC and BAC clones were used in standard PCR

reactions to determine clone overlap. Primer pair B9F2 was derived from

a fragment that was generated by digesting BAC5 with BamHI and then

subcloning into the pUC19 vector. This clone can be hit by a primer pair

10   derived form the T7 end of BAC7. Single-strand conformation

polymorphisms (SSCP) were tested on 6% MDE acrylamide (FMC

Bioproducts) gels at 40°C.

Cloning of the zebrafish N2B domain

Long RT-PCR was performed to amplify the N2B domain from

15   adult zebrafish heart mRNA extracts. mRNA was extracted from pools of

ten zebrafish adult hearts using TRIzole reagent (GibcolBRL), as

described. The cDNA was synthesized using SuperScripTMII RNase H-

Reverse Transcriptase (GibcoBRL) and then treated with RNase H. The

primer is derived from EST3: I19R1:

20   5'- TTTGAACCACTTGAAGGTCACACCAGG (SEQ ID NO:5).

Long-PCR was performed using Expand 20kbPlus PCR System (Roch) as

described. The primer pairs are:

I14F1: 5'- GCTAAGAATGACTATGGAGTTGCCACAAGC (SEQ ID

NO:6)

25   I19R2: 5'- TGAACCACTTGAAGGTCACACCAGGAG (SEQ ID NO:7)

The 4.6 kb product was subcloned using TOPO TA Cloning Kit (Invitrogen) as described. The sequence was determined by primer walking. Forty eight reads were aligned by Phred/Phrad software to get a large contig that contains only one reading frame with around three fold

5   coverage.

To amplify the N2B region from the homozygous mutant zebrafish embryos, three overlapping primer pairs were designed according to the adult N2B sequence. The contamination from the skeletal muscle specific titin isoform was thus eliminated. mRNA was extracted from pools of ten

10   zebrafish day 2 embryos using TRIzole reagent (GibcoBRL) as described. Sequencing results indicated that the embryonic heart titin contain one less IG domain in the area.

Identification of the point mutation

N2B domains from the homozygous mutant embryos were further

15   amplified by primer pairs that generate six overlapping PCR products sized between 0.6 kb and about 1 kb. RNA mismatch analysis was performed using MutationScreenerTM (Ambion) according to the manufacture's protocol. A mismatch was identified between *pikm171* and *pikm242* using the primer pairs:

20   P238FT:

5'-TAATACGACTCACTATAGGGAGGGACACTCAGAGACCATAG (SEQ ID NO:8)

P3785RT: 5'-

TAATACGACTCACTATAGGGGTCTGAGGATACTCGCCTTC (SEQ

25   ID NO:9). Sequencing results indicate a T->G non-sense mutation in the cDNA from homozygous *pikm171* embryos.

Genomic sequence in this region was amplified using the primer pair:

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P238F: 5'-AGGGACACTCAGAGACCATAG (SEQ ID NO:10)

P341R: 5'- GGCAATGTTACTCTCTGTTGAG (SEQ ID NO:11)

and sent out directly for sequencing after purification using the Geneclean

Spin Kit (BIO101).

5 Electron Microscopy

Forty eight hour embryos were fixed overnight at 4°C in 1.5%

glutaraldehyde, 1% paraformaldehyde, 70 mM $NaPO_4$ pH 7.2, 3%

Sucrose. They were then washed 3 times for 5 minutes each in 0.1M

cacodylate buffer, pH 7.4.

10 Other Embodiments

Although the present invention has been described with reference to

preferred embodiments, one skilled in the art can easily ascertain its

essential characteristics and without departing from the spirit and scope

thereof, can make various changes and modifications of the invention to

15 adapt it to various usages and conditions. Those skilled in the art will

recognize or be able to ascertain using no more than routine

experimentation, many equivalents to the specific embodiments of the

invention described herein. Such equivalents are intended to be

encompassed in the scope of the present invention.

20 All publications and patents mentioned in this specification are

hereby incorporated by reference.

What is claimed is:

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Claims

1. A method of determining whether a test subject has, or is at risk of developing, a titin-related disease or condition, said method comprising analyzing a nucleic acid molecule of a sample from the test subject to
5 determine whether the test subject has a mutation in a *titin* gene, wherein the presence of said mutation is an indication that said test subject has, or is at risk of developing, a titin-related disease.

2. The method of claim 1, further comprising the step of using nucleic acid molecule primers specific for the *titin* gene for nucleic acid
10 molecule amplification of the *titin* gene by the polymerase chain reaction.

3. The method of claim 1, further comprising the step of sequencing *titin* nucleic acid molecules from said test subject.

4. The method of claim 1, wherein said test subject is a mammal.

5. The method of claim 1, wherein said test subject is human.

15   6. The method of claim 1, wherein said disease or condition is heart failure.

7. The method of claim 1, wherein said mutation is the *pickwick* mutation.

8. A method for identifying a compound that can be used to treat or to prevent heart failure, said method comprising contacting an organism comprising a *titin* mutation and having a phenotype characteristic of heart failure with said compound, and determining the effect of said compound

5 on said phenotype, wherein detection of an improvement in said phenotype indicates the identification of a compound that can be used to treat or to prevent heart failure.

9. The method of claim 8, wherein said organism is a zebrafish.

10. The method of claim 8, wherein said *titin* mutation is the

10 *pickwick* mutation.

11. A method of treating or preventing heart failure in a patient, said method comprising administering to said patient a compound identified using the method of claim 8.

12. The method of claim 11, wherein said patient has a mutation in

15 the *titin* gene.

13. The method of claim 12, wherein said mutation is the *pickwick* mutation.

14. A non-human animal comprising a mutation in a *titin* gene.

15. The non-human animal of claim 14, wherein the non-human

20 animal is a zebrafish.

16. The non-human animal of claim 14, wherein the mutation is in a cardiac-specific exon of said *titin* gene.

17. The non-human animal of claim 16, wherein the mutation is in the N2B exon of said *titin* gene.

5   18. The non-human animal of claim 14, wherein the mutation results in the presence of a stop codon in said *titin* gene.

19. The non-human animal of claim 14, wherein the mutation is the *pickwick* mutation.
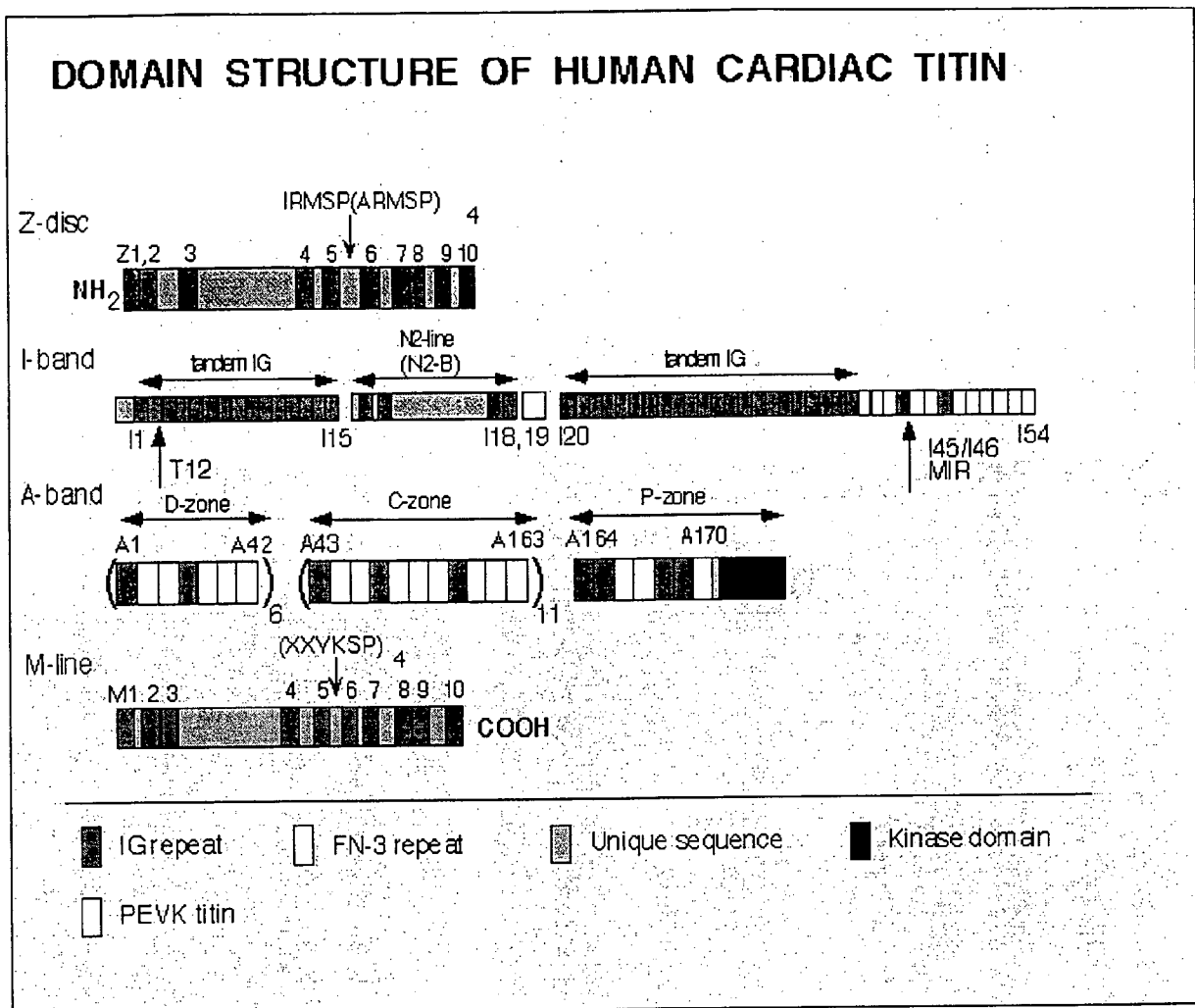
Fig. 1 Domain structure of the titin filament.

SEQUENCE LISTING

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Pro Val Pro Glu Val Ser Trp Phe Arg Asp Gly Gln Val Ile Ser Thr
        35                  40                  45
Ser Thr Leu Pro Gly Val Gln Ile Ser Phe Ser Asp Gly Arg Ala Lys
    50                  55                  60
Leu Thr Ile Pro Ala Val Thr Lys Ala Asn Ser Gly Arg Tyr Ser Leu
65                  70                  75                  80
Lys Ala Thr Asn Gly Ser Gly Gln Ala Thr Ser Thr Ala Glu Leu Leu
                85                  90                  95
Val Lys Ala Glu Thr Ala Pro Pro Asn Phe Val Gln Arg Leu Gln Ser
            100                 105                 110
Met Thr Val Arg Gln Gly Ser Gln Val Arg Leu Gln Val Arg Val Thr
        115                 120                 125
Gly Ile Pro Thr Pro Val Val Lys Phe Tyr Arg Asp Gly Ala Glu Ile
        130                 135                 140
Gln Ser Ser Leu Asp Phe Gln Ile Ser Gln Glu Gly Asp Leu Tyr Ser
145                 150                 155                 160
Leu Leu Ile Ala Glu Ala Tyr Pro Glu Asp Ser Gly Thr Tyr Ser Val
                165                 170                 175
Asn Ala Thr Asn Ser Val Gly Arg Ala Thr Ser Thr Ala Glu Leu Leu
            180                 185                 190
Val Gln Gly Glu Glu Glu Val Pro Ala Lys Lys Thr Lys Thr Ile Val
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Ser Thr Ala Gln Ile Ser Glu Ser Arg Gln Thr Arg Ile Glu Lys Lys
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Ile Asp Gly Ala Ala Gly Gln Gln Leu Pro His Lys Thr Pro Pro Arg
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Ile Pro Pro Lys Pro Lys Ser Arg Ser Pro Thr Pro Pro Ser Ile Ala
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Ala Lys Ala Gln Leu Ala Arg Gln Gln Ser Pro Ser Pro Ile Arg His
            275                 280                 285
Ser Pro Ser Pro Val Arg His Val Arg Ala Pro Thr Pro Ser Pro Val
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Arg Ser Val Ser Pro Ala Ala Arg Ile Ser Thr Ser Pro Ile Arg Ser
305                 310                 315                 320
Val Arg Ser Pro Leu Leu Met Arg Lys Thr Gln Ala Ser Thr Val Ala
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Thr Gly Pro Glu Val Pro Pro Pro Trp Lys Gln Glu Gly Tyr Val Ala
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Ser Ser Ser Glu Ala Glu Met Arg Glu Thr Thr Leu Thr Thr Ser Thr
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Gln Ile Arg Thr Glu Glu Arg Trp Glu Gly Arg Tyr Gly Val Gln Glu
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Gln Val Thr Ile Ser Gly Ala Ala Gly Ala Ala Ala Ser Val Ser Ala
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Ser Ala Ser Tyr Ala Ala Glu Ala Val Ala Thr Gly Ala Lys Glu Val
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Lys Gln Asp Ala Asp Lys Ser Ala Ala Val Ala Thr Val Val Ala Ala
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Thr Ala Gln Arg Thr Thr Thr Thr Ala Val His Ile Gln Pro Ala Gln
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Glu Gln Val Arg Lys Glu Ala Glu Lys Thr Ala Val Thr Lys Val Val
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Val Ala Ala Asp Lys Ala Lys Glu Gln Glu Leu Lys Ser Arg Thr Lys
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Glu Ile Ile Thr Thr Lys Gln Glu Gln Met His Val Thr His Glu Gln
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Ile Arg Lys Glu Thr Glu Lys Thr Phe Val Pro Lys Val Val Ile Ser
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Lys Thr Val Val Pro Lys Val Ile Val Ala Thr Pro Lys Val Lys Glu
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Gln Asp Leu Val Ser Arg Gly Arg Glu Gly Ile Thr Thr Lys Arg Glu
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Gln Val Gln Ile Thr Gln Glu Lys Met Arg Lys Glu Ala Glu Lys Thr
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Ala Leu Ser Thr Ile Ala Val Ala Thr Ala Lys Ala Lys Glu Gln Glu
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Gln Val Thr His Gly Lys Val Asp Val Gly Lys Lys Ala Glu Ala Val
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Ala Thr Val Val Ala Ala Val Asp Gln Ala Arg Val Arg Glu Pro Arg
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Glu Pro Gly His Leu Glu Glu Ser Tyr Ala Gln Gln Thr Thr Leu Glu
    675                 680                 685
Tyr Gly Tyr Lys Glu Arg Ile Ser Ala Ala Lys Val Ala Glu Pro Pro
    690                 695                 700
Gln Arg Pro Ala Ser Glu Pro His Val Val Pro Lys Ala Val Lys Pro
705                 710                 715                 720
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Lys Gly Met His Ile Ser Ser Gln Ile Lys Lys Thr Thr Asp Leu Thr
            740                 745                 750
Thr Glu Arg Leu Val His Val Asp Lys Arg Pro Arg Thr Ala Ser Pro
            755                 760                 765
His Phe Thr Val Ser Lys Ile Ser Val Pro Lys Thr Glu His Gly Tyr
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Glu Ala Ser Ile Ala Gly Ser Ala Ile Ala Thr Leu Gln Lys Glu Leu
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Ser Ala Thr Ser Ser Ala Gln Lys Ile Thr Lys Ser Val Lys Ala Pro
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Thr Val Lys Pro Ser Glu Thr Arg Val Arg Ala Glu Pro Thr Pro Leu
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Pro Gln Phe Pro Phe Ala Asp Thr Pro Asp Thr Tyr Lys Ser Glu Ala
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Gly Val Glu Val Lys Lys Glu Val Gly Val Ser Ile Thr Gly Thr Thr
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Val Arg Glu Glu Arg Phe Glu Val Leu His Gly Arg Glu Ala Lys Val
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Thr Glu Thr Ala Arg Val Pro Ala Pro Val Glu Ile Pro Val Thr Pro
            885                 890                 895
Pro Thr Leu Val Ser Gly Leu Lys Asn Val Thr Val Ile Glu Gly Glu
            900                 905                 910
Ser Val Thr Leu Glu Cys His Ile Ser Gly Tyr Pro Ser Pro Thr Val
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Thr Trp Tyr Arg Glu Asp Tyr Gln Ile Glu Ser Ser Ile Asp Phe Gln
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Ile Thr Phe Gln Ser Gly Ile Ala Arg Leu Met Ile Arg Glu Ala Phe
945                 950                 955                 960
Ala Glu Asp Ser Gly Arg Phe Thr Cys Ser Ala Val Asn Glu Ala Gly
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Thr Val Ser Thr Ser Cys Tyr Leu Ala Val Gln Val Ser Glu Glu Phe
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Cys Gln Val Gly Gly Asn Pro Lys Pro His Val Tyr Trp Lys Lys Ser
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Glu Lys Glu Tyr Glu Lys Glu Gln Ala Leu Ile Arg Lys Lys Met Ala
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Lys Asp Thr Val Val Val Arg Thr Tyr Val Glu Asp Gln Glu Phe His
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Ile Ser Ser Phe Glu Glu Arg Leu Ile Lys Glu Ile Glu Tyr Arg Ile
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Leu Arg Ile Lys Asn Tyr Arg Ile Leu Glu Gly Met Gly Val Thr Phe
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His Cys Lys Met Ser Gly Tyr Pro Leu Pro Lys Ile Ala Trp Tyr Lys
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Asp Gly Lys Arg Ile Lys His Gly Glu Arg Tyr Gln Met Asp Phe Leu
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Gln Asp Gly Arg Ala Ser Leu Arg Ile Pro Val Val Leu Pro Glu Asp
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Glu Gly Ile Tyr Thr Ala Phe Ala Ser Asn Ile Lys Gly Asn Ala Ile
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Cys Ser Gly Lys Leu Tyr Val Glu Pro Ala Ala Pro Leu Gly Ala Pro
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His Lys Tyr Pro Lys Ile Arg Ile Glu Gly Thr Lys Gly Glu Ala Ala
        1555                1560                1565
Leu Lys Ile Asp Ser Thr Val Ser Gln Asp Ser Ala Trp Tyr Thr Ala
    1570                1575                1580
Thr Ala Ile Asn Lys Ala Gly Arg Asp Thr Thr Arg Cys Lys Val Asn
1585                1590                1595                1600
Val Glu Val Glu Phe Ala Glu Pro Glu Pro Glu Arg Lys Leu Ile Ile
            1605                1610                1615
Pro Arg Gly Thr Tyr Arg Ala Lys Glu Ile Ala Ala Pro Glu Leu Glu
        1620                1625                1630
Pro Leu His Leu Arg Tyr Gly Gln Glu Gln Trp Glu Glu Gly Asp Leu
        1635                1640                1645
Tyr Asp Lys Glu Lys Gln Gln Lys Pro Phe Phe Lys Lys Lys Leu Thr
    1650                1655                1660
Ser Leu Arg Leu Lys Arg Phe Gly Pro Ala His Phe Glu Cys Arg Leu
1665                1670                1675                1680
Thr Pro Ile Ser Asp Pro Thr Met Val Val Glu Trp Leu His Asp Gly
            1685                1690                1695
Lys Pro Leu Glu Ala Ala Asn Arg Leu Arg Met Ile Asn Glu Phe Gly
        1700                1705                1710
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Tyr Cys Ser Leu Asp Tyr Gly Val Ala Tyr Ser Arg Asp Ser Gly Ile
    1715                   1720                   1725
Ile Thr Cys Arg Ala Thr Asn Lys Tyr Gly Thr Asp His Thr Ser Ala
    1730                   1735                   1740
Thr Leu Ile Val Lys Asp Glu Lys Ser Leu Val Glu Glu Ser Gln Leu
1745                   1750                   1755                   1760
Pro Glu Gly Arg Lys Gly Leu Gln Arg Ile Glu Glu Leu Glu Arg Met
                1765                   1770                   1775
Ala His Glu Gly Ala Leu Thr Gly Val Thr Thr Asp Gln Lys Glu Lys
            1780                   1785                   1790
Gln Lys Pro Asp Ile Val Leu Tyr Pro Glu Pro Val Arg Val Leu Glu
        1795                   1800                   1805
Gly Glu Thr Ala Arg Phe Arg Cys Arg Val Thr Gly Tyr Pro Gln Pro
    1810                   1815                   1820
Lys Val Asn Trp Tyr Leu Asn Gly Gln Leu Ile Arg Lys Ser Lys Arg
1825                   1830                   1835                   1840
Phe Arg Val Arg Tyr Asp Gly Ile His Tyr Leu Asp Ile Val Asp Cys
                1845                   1850                   1855
Lys Ser Tyr Asp Thr Gly Glu Val Lys Val Thr Ala Glu Asn Pro Glu
            1860                   1865                   1870
Gly Val Ile Glu His Lys Val Lys Leu Glu Ile Gln Gln Arg Glu Asp
        1875                   1880                   1885
Phe Arg Ser Val Leu Arg Arg Ala Pro Glu Pro Arg Pro Glu Phe His
    1890                   1895                   1900
Val His Glu Pro Gly Lys Leu Gln Phe Glu Val Gln Lys Val Asp Arg
1905                   1910                   1915                   1920
Pro Val Asp Thr Thr Glu Thr Lys Glu Val Val Lys Leu Lys Arg Ala
                1925                   1930                   1935
Glu Arg Ile Thr His Glu Lys Val Pro Glu Glu Ser Glu Glu Leu Arg
            1940                   1945                   1950
Ser Lys Phe Lys Arg Arg Thr Glu Glu Gly Tyr Tyr Glu Ala Ile Thr
        1955                   1960                   1965
Ala Val Glu Leu Lys Ser Arg Lys Lys Asp Glu Ser Tyr Glu Glu Leu
    1970                   1975                   1980
Leu Arg Lys Thr Lys Asp Glu Leu Leu His Trp Thr Lys Glu Leu Thr
1985                   1990                   1995                   2000
Glu Glu Glu Lys Lys Ala Leu Ala Glu Glu Gly Lys Ile Thr Ile Pro
                2005                   2010                   2015
Thr Phe Lys Pro Asp Lys Ile Glu Leu Ser Pro Ser Met Glu Ala Pro
            2020                   2025                   2030
Lys Ile Phe Glu Arg Ile Gln Ser Gln Thr Val Gly Gln Gly Ser Asp
    2035                   2040                   2045
Ala His Phe Arg Val Arg Val Val Gly Lys Pro Asp Pro Glu Cys Glu
    2050                   2055                   2060
Trp Tyr Lys Asn Gly Val Lys Ile Glu Arg Ser Asp Arg Ile Tyr Trp
2065                   2070                   2075                   2080
Tyr Trp Pro Glu Asp Asn Val Cys Glu Leu Val Ile Arg Asp Val Thr
                2085                   2090                   2095
Ala Glu Asp Ser Ala Ser Ile Met Val Lys Ala Ile Asn Ile Ala Gly
            2100                   2105                   2110
Glu Thr Ser Ser His Ala Phe Leu Leu Val Gln Ala Lys Gln Leu Ile
        2115                   2120                   2125
Thr Phe Thr Gln Glu Leu Gln Asp Val Val Ala Lys Glu Lys Asp Thr
    2130                   2135                   2140
Met Ala Thr Phe Glu Cys Glu Thr Ser Glu Pro Phe Val Lys Val Lys
2145                   2150                   2155                   2160
Trp Tyr Lys Asp Gly Met Glu Val His Glu Gly Asp Lys Tyr Arg Met
                2165                   2170                   2175
His Ser Asp Arg Lys Val His Phe Leu Ser Ile Leu Thr Ile Asp Thr
            2180                   2185                   2190
Ser Asp Ala Glu Asp Tyr Ser Cys Val Leu Val Glu Asp Glu Asn Val
        2195                   2200                   2205
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Lys Thr Thr Ala Lys Leu Ile Val Glu Gly Ala Val Val Glu Phe Val
    2210                2215                2220
Lys Glu Leu Gln Asp Ile Glu Val Pro Glu Ser Tyr Ser Gly Glu Leu
2225                2230                2235                    2240
Glu Cys Ile Val Ser Pro Glu Asn Ile Glu Gly Lys Trp Tyr His Asn
            2245                2250                2255
Asp Val Glu Leu Lys Ser Asn Gly Lys Tyr Thr Ile Thr Ser Arg Arg
        2260                2265                2270
Gly Arg Gln Asn Leu Thr Val Lys Asp Val Thr Lys Glu Asp Gln Gly
        2275                2280                2285
Glu Tyr Ser Phe Val Ile Asp Gly Lys Lys Thr Thr Cys Lys Leu Lys
    2290                2295                2300
Met Lys Pro Arg Pro Ile Ala Ile Leu Gln Gly Leu Ser Asp Gln Lys
2305                2310                2315                    2320
Val Cys Glu Gly Asp Ile Val Gln Leu Glu Val Lys Val Ser Leu Glu
            2325                2330                2335
Ser Val Glu Gly Val Trp Met Lys Asp Gly Gln Glu Val Gln Pro Ser
            2340                2345                2350
Asp Arg Val His Ile Val Ile Asp Lys Gln Ser His Met Leu Leu Ile
        2355                2360                2365
Glu Asp Met Thr Lys Glu Asp Ala Gly Asn Tyr Ser Phe Thr Ile Pro
    2370                2375                2380
Ala Leu Gly Leu Ser Thr Ser Gly Arg Val Ser Val Tyr Ser Val Asp
2385                2390                2395                    2400
Val Ile Thr Pro Leu Lys Asp Val Asn Val Ile Glu Gly Thr Lys Ala
            2405                2410                2415
Val Leu Glu Cys Lys Val Ser Val Pro Asp Val Thr Ser Val Lys Trp
            2420                2425                2430
Tyr Leu Asn Asp Glu Gln Ile Lys Pro Asp Asp Arg Val Gln Ala Ile
            2435                2440                2445
Val Lys Gly Thr Lys Gln Arg Leu Val Ile Asn Arg Thr His Ala Ser
    2450                2455                2460
Asp Glu Gly Pro Tyr Lys Leu Ile Val Gly Arg Val Glu Thr Asn Cys
2465                2470                2475                    2480
Asn Leu Ser Val Glu Lys Ile Lys Ile Ile Arg Gly Leu Arg Asp Leu
            2485                2490                2495
Thr Cys Thr Glu Thr Gln Asn Val Val Phe Glu Val Glu Leu Ser His
            2500                2505                2510
Ser Gly Ile Asp Val Leu Trp Asn Phe Lys Asp Lys Glu Ile Lys Pro
        2515                2520                2525
Ser Ser Lys Tyr Lys Ile Glu Ala His Gly Lys Ile Tyr Lys Leu Thr
    2530                2535                2540
Val Leu Asn Met Met Lys Asp Asp Glu Gly Lys Tyr Thr Phe Tyr Ala
2545                2550                2555                    2560
Gly Glu Asn Met Thr Ser Gly Lys Leu Thr Val Ala Gly Gly Ala Ile
            2565                2570                2575
Ser Lys Pro Leu Thr Asp Gln Thr Val Ala Glu Ser Gln Glu Ala Val
        2580                2585                2590
Phe Glu Cys Glu Val Ala Asn Pro Asp Ser Lys Gly Glu Trp Leu Arg
        2595                2600                2605
Asp Gly Lys His Leu Pro Leu Thr Asn Asn Ile Arg Ser Glu Ser Asp
    2610                2615                2620
Gly His Lys Arg Arg Leu Ile Ile Ala Ala Thr Lys Leu Asp Asp Ile
2625                2630                2635                    2640
Gly Glu Tyr Thr Tyr Lys Val Ala Thr Ser Lys Thr Ser Ala Lys Leu
            2645                2650                2655
Lys Val Glu Ala Val Lys Ile Lys Lys Thr Leu Lys Asn Leu Thr Val
            2660                2665                2670
Thr Glu Thr Gln Asp Ala Val Phe Thr Val Glu Leu Thr His Pro Asn
        2675                2680                2685
Val Lys Gly Val Gln Trp Ile Lys Asn Gly Val Val Leu Glu Ser Asn
    2690                2695                2700
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Glu Lys Tyr Ala Ile Ser Val Lys Gly Thr Ile Tyr Ser Leu Arg Ile
2705                2710                2715                    2720
Lys Asn Cys Ala Ile Val Asp Glu Ser Val Tyr Gly Phe Arg Leu Gly
                2725                2730                2735
Arg Leu Gly Ala Ser Ala Arg Leu His Val Glu Thr Val Lys Ile Ile
            2740                2745                2750
Lys Lys Pro Lys Asp Val Thr Ala Leu Glu Asn Ala Thr Val Ala Phe
            2755                2760                2765
Glu Val Ser Val Ser His Asp Thr Val Pro Val Lys Trp Phe His Lys
    2770                2775                2780
Ser Val Glu Ile Lys Pro Ser Asp Lys His Arg Leu Val Ser Glu Arg
2785                2790                2795                    2800
Lys Val His Lys Leu Met Leu Gln Asn Ile Ser Pro Ser Asp Ala Gly
                2805                2810                2815
Glu Tyr Thr Ala Val Val Gly Gln Leu Glu Cys Lys Ala Lys Leu Phe
                2820                2825                2830
Val Glu Thr Leu His Ile Thr Lys Thr Met Lys Asn Ile Glu Val Pro
            2835                2840                2845
Glu Thr Lys Thr Ala Ser Phe Glu Cys Glu Val Ser His Phe Asn Val
    2850                2855                2860
Pro Ser Met Trp Leu Lys Asn Gly Val Glu Ile Glu Met Ser Glu Lys
2865                2870                2875                    2880
Phe Lys Ile Val Val Gln Gly Lys Leu His Gln Leu Ile Ile Met Asn
                2885                2890                2895
Thr Ser Thr Glu Asp Ser Ala Glu Tyr Thr Phe Val Cys Gly Asn Asp
            2900                2905                2910
Gln Val Ser Ala Thr Leu Thr Val Thr Pro Ile Met Ile Thr Ser Met
    2915                2920                2925
Leu Lys Asp Ile Asn Ala Glu Glu Lys Asp Thr Ile Thr Phe Glu Val
    2930                2935                2940
Thr Val Asn Tyr Glu Gly Ile Ser Tyr Lys Trp Leu Lys Asn Gly Val
2945                2950                2955                    2960
Glu Ile Lys Ser Thr Asp Lys Cys Gln Met Arg Thr Lys Lys Leu Thr
            2965                2970                2975
His Ser Leu Asn Ile Arg Asn Val His Phe Gly Asp Ala Ala Asp Tyr
            2980                2985                2990
Thr Phe Val Ala Gly Lys Ala Thr Ser Thr Ala Thr Leu Tyr Val Glu
    2995                3000                3005
Ala Arg His Ile Glu Phe Arg Lys His Ile Lys Asp Ile Lys Val Leu
    3010                3015                3020
Glu Lys Lys Arg Ala Met Phe Glu Cys Glu Val Ser Glu Pro Asp Ile
3025                3030                3035                    3040
Thr Val Gln Trp Met Lys Asp Asp Gln Glu Leu Gln Ile Thr Asp Arg
            3045                3050                3055
Ile Lys Ile Gln Lys Glu Lys Tyr Val His Arg Leu Leu Ile Pro Ser
    3060                3065                3070
Thr Arg Met Ser Asp Ala Gly Lys Tyr Thr Val Val Ala Gly Gly Asn
    3075                3080                3085
Val Ser Thr Ala Lys Leu Phe Val Glu Gly Arg Asp Val Arg Ile Arg
    3090                3095                3100
Ser Ile Lys Lys Glu Val Gln Val Ile Glu Lys Gln Arg Ala Val Val
3105                3110                3115                    3120
Glu Phe Glu Val Asn Glu Asp Asp Val Asp Ala His Trp Tyr Lys Asp
                3125                3130                3135
Gly Ile Glu Ile Asn Phe Gln Val Gln Glu Arg His Lys Tyr Val Val
            3140                3145                3150
Glu Arg Arg Ile His Arg Met Phe Ile Ser Glu Thr Arg Gln Ser Asp
        3155                3160                3165
Ala Gly Glu Tyr Thr Phe Val Ala Gly Arg Asn Arg Ser Ser Val Thr
    3170                3175                3180
Leu Tyr Val Asn Ala Pro Glu Pro Pro Gln Val Leu Gln Glu Leu Gln
3185                3190                3195                    3200
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Pro Val Thr Val Gln Ser Gly Lys Pro Ala Arg Phe Cys Ala Met Ile
              3205                3210                3215
Ser Gly Arg Pro Gln Pro Lys Ile Ser Trp Tyr Lys Glu Glu Gln Leu
          3220                3225                3230
Leu Ser Thr Gly Phe Lys Cys Lys Phe Leu His Asp Gly Gln Glu Tyr
          3235                3240                3245
Thr Leu Leu Leu Ile Glu Ala Phe Pro Glu Asp Ala Ala Val Tyr Thr
    3250                3255                3260
Cys Glu Ala Lys Asn Asp Tyr Gly Val Ala Thr Thr Ser Ala Ser Leu
3265                3270                3275                3280
Ser Val Glu Val Pro Glu Val Val Ser Pro Asp Gln Glu Met Pro Val
              3285                3290                3295
Tyr Pro Pro Ala Ile Ile Thr Pro Leu Gln Asp Thr Val Thr Ser Glu
          3300                3305                3310
Gly Gln Pro Ala Arg Phe Gln Cys Arg Val Ser Gly Thr Asp Leu Lys
          3315                3320                3325
Val Ser Trp Tyr Ser Lys Asp Lys Lys Ile Lys Pro Ser Arg Phe Phe
    3330                3335                3340
Arg Met Thr Gln Phe Glu Asp Thr Tyr Gln Leu Glu Ile Ala Glu Ala
3345                3350                3355                3360
Tyr Pro Glu Asp Glu Gly Thr Tyr Thr Phe Val Ala Asn Asn Ala Val
              3365                3370                3375
Gly Gln Val Ser Ser Thr Ala Asn Leu Ser Leu Glu Ala Pro Glu Ser
          3380                3385                3390
Ile Leu His Glu Arg Ile Glu Gln Glu Ile Glu Met Glu Met Lys Glu
          3395                3400                3405
Phe Ser Ser Ser Phe Leu Ser Ala Glu Glu Glu Gly Leu His Ser Ala
    3410                3415                3420
Glu Leu Gln Leu Ser Lys Ile Asn Glu Thr Leu Glu Leu Leu Ser Glu
3425                3430                3435                3440
Ser Pro Val Tyr Pro Thr Lys Phe Asp Ser Glu Lys Glu Gly Thr Gly
              3445                3450                3455
Pro Ile Phe Ile Lys Glu Val Ser Asn Ala Asp Ile Ser Met Gly Asp
          3460                3465                3470
Val Ala Thr Leu Ser Val Thr Val Ile Gly Ile Pro Lys Pro Lys Ile
          3475                3480                3485
Gln Trp Phe Phe Asn Gly Val Leu Leu Thr Pro Ser Ala Asp Tyr Lys
          3490                3495                3500
Phe Val Phe Asp Gly Asp Asp His Ser Leu Ile Ile Leu Phe Thr Lys
3505                3510                3515                3520
Leu Glu Asp Glu Gly Glu Tyr Thr Cys Met Ala Ser Asn Asp Tyr Gly
              3525                3530                3535
Lys Thr Ile Cys Ser Ala Tyr Leu Lys Ile Asn Ser Lys Gly Glu Gly
          3540                3545                3550
His Lys Asp Thr Glu Thr Glu Ser Ala Val Ala Lys Ser Leu Glu Lys
          3555                3560                3565
Leu Gly Gly Pro Cys Pro Pro His Phe Leu Lys Glu Leu Lys Pro Ile
    3570                3575                3580
Arg Cys Ala Gln Gly Leu Pro Ala Ile Phe Glu Tyr Thr Val Val Gly
3585                3590                3595                3600
Glu Pro Ala Pro Thr Val Thr Trp Phe Lys Glu Asn Lys Gln Leu Cys
          3605                3610                3615
Thr Ser Val Tyr Tyr Thr Ile Ile His Asn Pro Asn Gly Ser Gly Thr
          3620                3625                3630
Phe Ile Val Asn Asp Pro Gln Arg Glu Asp Ser Gly Leu Tyr Ile Cys
    3635                3640                3645
Lys Ala Glu Asn Met Leu Gly Glu Ser Thr Cys Ala Ala Glu Leu Leu
    3650                3655                3660
Val Leu Leu Glu Asp Thr Asp Met Thr Asp Thr Pro Cys Lys Ala Lys
3665                3670                3675                3680
Ser Thr Pro Glu Ala Pro Glu Asp Phe Pro Gln Thr Pro Leu Lys Gly
              3685                3690                3695
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Pro Ala Val Glu Ala Leu Asp Ser Glu Gln Glu Ile Ala Thr Phe Val
        3700                3705                3710
Lys Asp Thr Ile Leu Lys Ala Ala Leu Ile Thr Glu Glu Asn Gln Gln
        3715                3720                3725
Leu Ser Tyr Glu His Ile Ala Lys Ala Asn Glu Leu Ser Ser Gln Leu
        3730                3735                3740
Pro Leu Gly Ala Gln Glu Leu Gln Ser Ile Leu Glu Gln Asp Lys Leu
3745                3750                3755                3760
Thr Pro Glu Ser Thr Arg Glu Phe Leu Cys Ile Asn Gly Ser Ile His
        3765                3770                3775
Phe Gln Pro Leu Lys Glu Pro Ser Pro Asn Leu Gln Leu Gln Ile Val
        3780                3785                3790
Gln Ser Gln Lys Thr Phe Ser Lys Glu Gly Ile Leu Met Pro Glu Glu
        3795                3800                3805
Pro Glu Thr Gln Ala Val Leu Ser Asp Thr Glu Lys Ile Phe Pro Ser
3810                3815                3820
Ala Met Ser Ile Glu Gln Ile Asn Ser Leu Thr Val Glu Pro Leu Lys
3825                3830                3835                3840
Thr Leu Leu Ala Glu Pro Glu Gly Asn Tyr Pro Gln Ser Ser Ile Glu
        3845                3850                3855
Pro Pro Met His Ser Tyr Leu Thr Ser Val Ala Glu Glu Val Leu Ser
        3860                3865                3870
Leu Lys Glu Lys Thr Val Ser Asp Thr Asn Arg Glu Gln Arg Val Thr
        3875                3880                3885
Leu Gln Lys Gln Glu Ala Gln Ser Ala Leu Ile Leu Ser Gln Ser Leu
        3890                3895                3900
Ala Glu Gly His Val Glu Ser Leu Gln Ser Pro Asp Val Met Ile Ser
3905                3910                3915                3920
Gln Val Asn Tyr Glu Pro Leu Val Pro Ser Glu His Ser Cys Thr Glu
        3925                3930                3935
Gly Gly Lys Ile Leu Ile Glu Ser Ala Asn Pro Leu Glu Asn Ala Gly
        3940                3945                3950
Gln Asp Ser Ala Val Arg Ile Glu Glu Gly Lys Ser Leu Arg Phe Pro
        3955                3960                3965
Leu Ala Leu Glu Glu Lys Gln Val Leu Leu Lys Glu Glu His Ser Asp
        3970                3975                3980
Asn Val Val Met Pro Pro Asp Gln Ile Ile Glu Ser Lys Arg Glu Pro
3985                3990                3995                4000
Val Ala Ile Lys Lys Val Gln Glu Val Gln Gly Arg Asp Leu Leu Ser
        4005                4010                4015
Lys Glu Ser Leu Leu Ser Gly Ile Pro Glu Glu Gln Arg Leu Asn Leu
        4020                4025                4030
Lys Ile Gln Ile Cys Arg Ala Leu Gln Ala Ala Val Ala Ser Glu Gln
        4035                4040                4045
Pro Gly Leu Phe Ser Glu Trp Leu Arg Asn Ile Glu Lys Val Glu Val
4050                4055                4060
Glu Ala Val Asn Ile Thr Gln Glu Pro Arg His Ile Met Cys Met Tyr
4065                4070                4075                4080
Leu Val Thr Ser Ala Lys Ser Val Thr Glu Glu Val Thr Ile Ile Ile
        4085                4090                4095
Glu Asp Val Asp Pro Gln Met Ala Asn Leu Lys Met Glu Leu Arg Asp
        4100                4105                4110
Ala Leu Cys Ala Ile Ile Tyr Glu Glu Ile Asp Ile Leu Thr Ala Glu
        4115                4120                4125
Gly Pro Arg Ile Gln Gln Gly Ala Lys Thr Ser Leu Gln Glu Glu Met
        4130                4135                4140
Asp Ser Phe Ser Gly Ser Gln Lys Val Glu Pro Ile Thr Glu Pro Glu
4145                4150                4155                4160
Val Glu Ser Lys Tyr Leu Ile Ser Thr Glu Glu Val Ser Tyr Phe Asn
        4165                4170                4175
Val Gln Ser Arg Val Lys Tyr Leu Asp Ala Thr Pro Val Thr Lys Gly
        4180                4185                4190
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Val Ala Ser Ala Val Val Ser Asp Glu Lys Gln Asp Glu Ser Leu Lys
      4195                    4200                    4205
Pro Ser Glu Glu Lys Glu Glu Ser Ser Ser Glu Ser Gly Thr Glu Glu
      4210                    4215                    4220
Val Ala Thr Val Lys Ile Gln Glu Ala Glu Gly Gly Leu Ile Lys Glu
4225                    4230                    4235                    4240
Asp Gly Pro Met Ile His Thr Pro Leu Val Asp Thr Val Ser Glu Glu
              4245                    4250                    4255
Gly Asp Ile Val His Leu Thr Thr Ser Ile Thr Asn Ala Lys Glu Val
              4260                    4265                    4270
Asn Trp Tyr Phe Glu Asn Lys Leu Val Pro Ser Asp Glu Lys Phe Lys
      4275                    4280                    4285
Cys Leu Gln Asp Gln Asn Thr Tyr Thr Leu Val Ile Asp Lys Val Asn
      4290                    4295                    4300
Thr Glu Asp His Gln Gly Glu Tyr Val Cys Glu Ala Leu Asn Asp Ser
4305                    4310                    4315                    4320
Gly Lys Thr Ala Thr Ser Ala Lys Leu Thr Val Val Lys Arg Ala Ala
              4325                    4330                    4335
Pro Val Ile Lys Arg Lys Ile Glu Pro Leu Glu Val Ala Leu Gly His
              4340                    4345                    4350
Leu Ala Lys Phe Thr Cys Glu Ile Gln Ser Ala Pro Asn Val Arg Phe
              4355                    4360                    4365
Gln Trp Phe Lys Ala Gly Arg Glu Ile Tyr Glu Ser Asp Lys Cys Ser
      4370                    4375                    4380
Ile Arg Ser Ser Lys Tyr Ile Ser Ser Leu Glu Ile Leu Arg Thr Gln
4385                    4390                    4395                    4400
Val Val Asp Cys Gly Glu Tyr Thr Cys Lys Ala Ser Asn Glu Tyr Gly
              4405                    4410                    4415
Ser Val Ser Cys Thr Ala Thr Leu Thr Val Thr Val Pro Gly Gly Glu
              4420                    4425                    4430
Lys Lys Val Arg Lys Leu Leu Pro Glu Arg Lys Pro Glu Pro Lys Glu
      4435                    4440                    4445
Glu Val Val Leu Lys Ser Val Leu Arg Lys Arg Pro Glu Glu Glu Glu
      4450                    4455                    4460
Pro Lys Val Glu Pro Lys Lys Leu Glu Lys Val Lys Lys Pro Ala Val
4465                    4470                    4475                    4480
Pro Glu Pro Pro Pro Pro Lys Pro Val Glu Glu Val Glu Val Pro Thr
              4485                    4490                    4495
Val Thr Lys Arg Glu Arg Lys Ile Pro Glu Pro Thr Lys Val Pro Glu
      4500                    4505                    4510
Ile Lys Pro Ala Ile Pro Leu Pro Ala Pro Glu Pro Lys Pro Lys Pro
      4515                    4520                    4525
Glu Ala Glu Val Lys Thr Ile Lys Pro Pro Pro Val Glu Pro Glu Pro
      4530                    4535                    4540
Thr Pro Ile Ala Ala Pro Val Thr Val Pro Val Val Gly Lys Lys Ala
4545                    4550                    4555                    4560
Glu Ala Lys Ala Pro Lys Glu Glu Ala Ala Lys Pro Lys Gly Pro Ile
              4565                    4570                    4575
Lys Gly Val Pro Lys Lys Thr Pro Ser Pro Ile Glu Ala Glu Arg Arg
      4580                    4585                    4590
Lys Leu Arg Pro Gly Ser Gly Gly Glu Lys Pro Pro Asp Glu Ala Pro
      4595                    4600                    4605
Phe Thr Tyr Gln Leu Lys Ala Val Pro Leu Lys Phe Val Lys Glu Ile
      4610                    4615                    4620
Lys Asp Ile Ile Leu Thr Glu Ser Glu Phe Val Gly Ser Ser Ala Ile
4625                    4630                    4635                    4640
Phe Glu Cys Leu Val Ser Pro Ser Thr Ala Ile Thr Thr Trp Met Lys
              4645                    4650                    4655
Asp Gly Ser Asn Ile Arg Glu Ser Pro Lys His Arg Phe Ile Ala Asp
      4660                    4665                    4670
Gly Lys Asp Arg Lys Leu His Ile Ile Asp Val Gln Leu Ser Asp Ala
      4675                    4680                    4685
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Gly Glu Tyr Thr Cys Val Leu Arg Leu Gly Asn Lys Glu Lys Thr Ser
    4690                    4695                4700
Thr Ala Lys Leu Val Val Glu Glu Leu Pro Val Arg Phe Val Lys Thr
4705                    4710                4715                4720
Leu Glu Glu Glu Val Thr Val Val Lys Gly Gln Pro Leu Tyr Leu Ser
                4725                4730                4735
Cys Glu Leu Asn Lys Glu Arg Asp Val Val Trp Arg Lys Asp Gly Lys
            4740                4745                4750
Ile Val Val Glu Lys Pro Gly Arg Ile Val Pro Gly Val Ile Gly Leu
        4755                4760                4765
Met Arg Ala Leu Thr Ile Asn Asp Ala Asp Asp Thr Asp Ala Gly Thr
    4770                4775                4780
Tyr Thr Val Thr Val Glu Asn Ala Asn Asn Leu Glu Cys Ser Ser Cys
4785                4790                4795                4800
Val Lys Val Val Glu Val Ile Arg Asp Trp Leu Val Lys Pro Ile Arg
                4805                4810                4815
Asp Gln His Val Lys Pro Lys Gly Thr Ala Ile Phe Ala Cys Asp Ile
            4820                4825                4830
Ala Lys Asp Thr Pro Asn Ile Lys Trp Phe Lys Gly Tyr Asp Glu Ile
            4835                4840                4845
Pro Ala Glu Pro Asn Asp Lys Thr Glu Ile Leu Arg Asp Gly Asn His
    4850                4855                4860
Leu Tyr Leu Lys Ile Lys Asn Ala Met Pro Glu Asp Ile Ala Glu Tyr
4865                4870                4875                4880
Ala Val Glu Ile Glu Gly Lys Arg Tyr Pro Ala Lys Leu Thr Leu Gly
                4885                4890                4895
Glu Arg Glu Val Glu Leu Leu Lys Pro Ile Glu Asp Val Thr Ile Tyr
            4900                4905                4910
Glu Lys Glu Ser Ala Ser Phe Asp Ala Glu Ile Ser Glu Ala Asp Ile
            4915                4920                4925
Pro Gly Gln Trp Lys Leu Lys Gly Glu Leu Leu Arg Pro Ser Pro Thr
            4930                4935                4940
Cys Glu Ile Lys Ala Glu Gly Gly Lys Arg Phe Leu Thr Leu His Lys
4945                4950                4955                4960
Val Lys Leu Asp Gln Ala Gly Glu Val Leu Tyr Gln Ala Leu Asn Ala
                4965                4970                4975
Ile Thr Thr Ala Ile Leu Thr Val Lys Glu Ile Glu Leu Asp Phe Ala
            4980                4985                4990
Val Pro Leu Lys Asp Val Thr Val Pro Glu Arg Arg Gln Ala Arg Phe
        4995                5000                5005
Glu Cys Val Leu Thr Arg Glu Ala Asn Val Ile Trp Ser Lys Gly Pro
    5010                5015                5020
Asp Ile Ile Lys Ser Ser Asp Lys Phe Asp Ile Ile Ala Asp Gly Lys
5025                5030                5035                5040
Lys His Ile Leu Val Ile Asn Asp Ser Gln Phe Asp Asp Glu Gly Val
            5045                5050                5055
Tyr Thr Ala Glu Val Glu Gly Lys Lys Thr Ser Ala Arg Leu Phe Val
        5060                5065                5070
Thr Gly Ile Arg Leu Lys Phe Met Ser Pro Leu Glu Asp Gln Thr Val
    5075                5080                5085
Lys Glu Gly Glu Thr Ala Thr Phe Val Cys Glu Leu Ser His Glu Lys
    5090                5095                5100
Met His Val Val Trp Phe Lys Asn Asp Ala Lys Leu His Thr Ser Arg
5105                5110                5115                5120
Thr Val Leu Ile Ser Ser Glu Gly Lys Thr His Lys Leu Glu Met Lys
                5125                5130                5135
Glu Val Thr Leu Asp Asp Ile Ser Gln Ile Lys Ala Gln Val Lys Glu
            5140                5145                5150
Leu Ser Ser Thr Ala Gln Leu Lys Val Leu Glu Ala Asp Pro Tyr Phe
        5155                5160                5165
Thr Val Lys Leu His Asp Lys Thr Ala Val Glu Lys Asp Glu Ile Thr
    5170                5175                5180
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Leu Lys Cys Glu Val Ser Lys Asp Val Pro Val Lys Trp Phe Lys Asp
5185   5190   5195   5200
Gly Glu Glu Ile Val Pro Ser Pro Lys Tyr Ser Ile Lys Ala Asp Gly
            5205   5210   5215
Leu Arg Arg Ile Leu Lys Ile Lys Lys Ala Asp Leu Lys Asp Lys Gly
        5220   5225   5230
Glu Tyr Val Cys Asp Cys Gly Thr Asp Lys Thr Lys Ala Asn Val Thr
    5235   5240   . 5245
Val Glu Ala Arg Leu Ile Glu Val Glu Lys Pro Leu Tyr Gly Val Glu
    5250   5255   5260
Val Phe Val Gly Glu Thr Ala His Phe Glu Ile Glu Leu Ser Glu Pro
5265   5270   5275   5280
Asp Val His Gly Gln Trp Lys Leu Lys Gly Gln Pro Leu Thr Ala Ser
            5285   5290   5295
Pro Asp Cys Glu Ile Ile Glu Asp Gly Lys Lys His Ile Leu Ile Leu
        5300   5305   5310
His Asn Cys Gln Leu Gly Met Thr Gly Glu Val Ser Phe Gln Ala Ala
        5315   5320   5325
Asn Ala Lys Ser Ala Ala Asn Leu Lys Val Lys Glu Leu Pro Leu Ile
    5330   5335   5340
Phe Ile Thr Pro Leu Ser Asp Val Lys Val Phe Glu Lys Asp Glu Ala
5345   5350   5355   5360
Lys Phe Glu Cys Glu Val Ser Arg Glu Pro Lys Thr Phe Arg Trp Leu
            5365   5370   5375
Lys Gly Thr Gln Glu Ile Thr Gly Asp Asp Arg Phe Glu Leu Ile Lys
        5380   5385   5390
Asp Gly Thr Lys His Ser Met Val Ile Lys Ser Ala Ala Phe Glu Asp
    5395   5400   5405
Glu Ala Lys Tyr Met Phe Glu Ala Glu Asp Lys His Thr Ser Gly Lys
    5410   5415   5420
Leu Ile Ile Glu Gly Ile Arg Leu Lys Phe Leu Thr Pro Leu Lys Asp
5425   5430   5435   5440
Val Thr Ala Lys Glu Lys Glu Ser Ala Val Phe Thr Val Glu Leu Ser
            5445   5450   5455
His Asp Asn Ile Arg Val Lys Trp Phe Lys Asn Asp Gln Arg Leu His
        5460   5465   5470
Thr Thr Arg Ser Val Ser Met Gln Asp Glu Gly Lys Thr His Ser Ile
        5475   5480   5485
Thr Phe Lys Asp Leu Ser Ile Asp Asp Thr Ser Gln Ile Arg Val Glu
    5490   5495   5500
Ala Met Gly Met Ser Ser Glu Ala Lys Leu Thr Val Leu Glu Gly Asp
5505   5510   5515   5520
Pro Tyr Phe Thr Gly Lys Leu Gln Asp Tyr Thr Gly Val Glu Lys Asp
            5525   5530   5535
Glu Val Ile Leu Gln Cys Glu Ile Ser Lys Ala Asp Ala Pro Val Lys
        5540   5545   5550
Trp Phe Lys Asp Gly Lys Glu Ile Lys Pro Ser Lys Asn Ala Val Ile
        5555   5560   5565
Lys Thr Asp Gly Lys Lys Arg Met Leu Ile Leu Lys Lys Ala Leu Lys
    5570   5575   5580
Ser Asp Ile Gly Gln Tyr Thr Cys Asp Cys Gly Thr Asp Lys Thr Ser
5585   5590   5595   5600
Gly Lys Leu Asp Ile Glu Asp Arg Glu Ile Lys Leu Val Arg Pro Leu
            5605   5610   5615
His Ser Val Glu Val Met Glu Thr Glu Thr Ala Arg Phe Glu Thr Glu
        5620   5625   5630
Ile Ser Glu Asp Asp Ile His Ala Asn Trp Lys Leu Lys Gly Glu Ala
        5635   5640   5645
Leu Leu Gln Thr Pro Asp Cys Glu Ile Lys Glu Glu Gly Lys Ile His
    5650   5655   5660
Ser Leu Val Leu His Asn Cys Arg Leu Asp Gln Thr Gly Gly Val Asp
5665   5670   5675   5680

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Phe Gln Ala Ala Asn Val Lys Ser Ser Ala His Leu Arg Val Lys Pro
              5685                5690                5695
Arg Val Ile Gly Leu Leu Arg Pro Leu Lys Asp Val Thr Val Thr Ala
              5700                5705                5710
Gly Glu Thr Ala Thr Phe Asp Cys Glu Leu Ser Tyr Glu Asp Ile Pro
              5715                5720                5725
Val Glu Trp Tyr Leu Lys Gly Lys Lys Leu Glu Pro Ser Asp Lys Val
              5730                5735                5740
Val Pro Arg Ser Glu Gly Lys Val His Thr Leu Thr Leu Arg Asp Val
5745                5750                5755                5760
Lys Leu Glu Asp Ala Gly Glu Val Gln Leu Thr Ala Lys Asp Phe Lys
              5765                5770                5775
Thr His Ala Asn Leu Phe Val Lys Glu Pro Pro Val Glu Phe Thr Lys
              5780                5785                5790
Pro Leu Glu Asp Gln Thr Val Glu Glu Gly Ala Thr Ala Val Leu Glu
              5795                5800                5805
Cys Glu Val Ser Arg Glu Asn Ala Lys Val Lys Trp Phe Lys Asn Gly
    5810                5815                5820
Thr Glu Ile Leu Lys Ser Lys Lys Tyr Glu Ile Val Ala Asp Gly Arg
5825     ·          5830                5835                5840
Val Arg Lys Leu Val Ile His Asp Cys Thr Pro Glu Asp Ile Lys Thr
              5845                5850                5855
Tyr Thr Cys Asp Ala Lys Asp Phe Lys Thr Ser Cys Asn Leu Asn Val
              5860                5865                5870
Val Pro Pro His Val Glu Phe Leu Arg Pro Leu Thr Asp Leu Gln Val
              5875                5880                5885
Arg Glu Lys Glu Met Ala Arg Phe Glu Cys Glu Leu Ser Arg Glu Asn
    5890                5895                5900
Ala Lys Val Lys Trp Phe Lys Asp Gly Ala Glu Ile Lys Lys Gly Lys
5905                5910                5915                5920
Lys Tyr Asp Ile Ile Ser Lys Gly Ala Val Arg Ile Leu Val Ile Asn
              5925                5930                5935
Lys Cys Leu Leu Asp Asp Glu Ala Glu Tyr Ser Cys Glu Val Arg Thr
              5940                5945                5950
Ala Arg Thr Ser Gly Met Leu Thr Val Leu Glu Glu Glu Ala Val Phe
              5955                5960                5965
Thr Lys Asn Leu Ala Asn Ile Glu Val Ser Glu Thr Asp Thr Ile Lys
              5970                5975                5980
Leu Val Cys Glu Val Ser Lys Pro Gly Ala Glu Val Ile Trp Tyr Lys
5985                5990                5995                6000
Gly Asp Glu Glu Ile Ile Glu Thr Gly Arg Tyr Glu Ile Leu Thr Glu
              6005                6010                6015
Gly Arg Lys Arg Ile Leu Val Ile Gln Asn Ala His Leu Glu Asp Ala
              6020                6025                6030
Gly Asn Tyr Asn Cys Arg Leu Pro Ser Ser Arg Thr Asp Gly Lys Val
              6035                6040                6045
Lys Val His Glu Leu Ala Ala Glu Phe Ile Ser Lys Pro Gln Asn Leu
    6050                6055                6060
Glu Ile Leu Glu Gly Glu Lys Ala Glu Phe Val Cys Ser Ile Ser Lys
6065                6070                6075                6080
Glu Ser Phe Pro Val Gln Trp Lys Arg Asp Asp Lys Thr Leu Glu Ser
              6085                6090                6095
Gly Asp Lys Tyr Asp Val Ile Ala Asp Gly Lys Lys Arg Val Leu Val
              6100                6105                6110
Val Lys Asp Ala Thr Leu Gln Asp Met Gly Thr Tyr Val Val Met Val
              6115                6120                6125
Gly Ala Ala Arg Ala Ala Ala His Leu Thr Val Ile Glu Lys Leu Arg
    6130                6135                6140
Ile Val Val Pro Leu Lys Asp Thr Arg Val Lys Glu Gln Gln Glu Val
6145                6150                6155                6160
Val Phe Asn Cys Glu Val Asn Thr Glu Gly Ala Lys Ala Lys Trp Phe
              6165                6170                6175
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Arg Asn Glu Glu Ala Ile Phe Asp Ser Ser Lys Tyr Ile Ile Leu Gln
        6180                6185                    6190
Lys Asp Leu Val Tyr Thr Leu Arg Ile Arg Asp Ala His Leu Asp Asp
        6195                6200                    6205
Gln Ala Asn Tyr Asn Val Ser Leu Thr Asn His Arg Gly Glu Asn Val
        6210                6215                    6220
Lys Ser Ala Ala Asn Leu Ile Val Glu Glu Glu Asp Leu Arg Ile Val
6225                6230                    6235                6240
Glu Pro Leu Lys Asp Ile Glu Thr Met Glu Lys Lys Ser Val Thr Phe
        6245                6250                    6255
Trp Cys Lys Val Asn Arg Leu Asn Val Thr Leu Lys Trp Thr Lys Asn
        6260                6265                    6270
Gly Glu Glu Val Pro Phe Asp Asn Arg Val Ser Tyr Arg Val Asp Lys
        6275                6280                    6285
Tyr Lys His Met Leu Thr Ile Lys Asp Cys Gly Phe Pro Asp Glu Gly
        6290                6295                    6300
Glu Tyr Ile Val Thr Ala Gly Gln Asp Lys Ser Val Ala Glu Leu Leu
6305                6310                    6315                6320
Ile Ile Glu Ala Pro Thr Glu Phe Val Glu His Leu Glu Asp Gln Thr
        6325                6330                    6335
Val Thr Glu Phe Asp Asp Ala Val Phe Ser Cys Gln Leu Ser Arg Glu
        6340                6345                    6350
Lys Ala Asn Val Lys Trp Tyr Arg Asn Gly Arg Glu Ile Lys Glu Gly
        6355                6360                    6365
Lys Lys Tyr Lys Phe Glu Lys Asp Gly Ser Ile His Arg Leu Ile Ile
        6370                6375                    6380
Lys Asp Cys Arg Leu Asp Asp Glu Cys Glu Tyr Ala Cys Gly Val Glu
6385                6390                    6395                6400
Asp Arg Lys Ser Arg Ala Arg Leu Phe Val Glu Glu Ile Pro Val Glu
        6405                6410                    6415
Ile Ile Arg Pro Pro Gln Asp Ile Leu Glu Ala Pro Gly Ala Asp Val
        6420                6425                    6430
Val Phe Leu Ala Glu Leu Asn Lys Asp Lys Val Glu Val Gln Trp Leu
        6435                6440                    6445
Arg Asn Asn Met Val Val Val Gln Gly Asp Lys His Gln Met Met Ser
        6450                6455                    6460
Glu Gly Lys Ile His Arg Leu Gln Ile Cys Asp Ile Lys Pro Arg Asp
6465                6470                    6475                6480
Gln Gly Glu Tyr Arg Phe Ile Ala Lys Asp Lys Glu Ala Arg Ala Lys
        6485                6490                    6495
Leu Glu Leu Ala Ala Ala Pro Lys Ile Lys Thr Ala Asp Gln Asp Leu
        6500                6505                    6510
Val Val Asp Val Gly Lys Pro Leu Thr Met Val Val Pro Tyr Asp Ala
        6515                6520                    6525
Tyr Pro Lys Ala Glu Ala Glu Trp Phe Lys Glu Asn Glu Pro Leu Ser
        6530                6535                    6540
Thr Lys Thr Ile Asp Thr Thr Ala Glu Gln Thr Ser Phe Arg Ile Leu
6545                6550                    6555                6560
Glu Ala Lys Lys Gly Asp Lys Gly Arg Tyr Lys Ile Val Leu Gln Asn
        6565                6570                    6575
Lys His Gly Lys Ala Glu Gly Phe Ile Asn Leu Lys Val Ile Asp Val
        6580                6585                    6590
Pro Gly Pro Val Arg Asn Leu Glu Val Thr Glu Thr Phe Asp Gly Glu
        6595                6600                    6605
Val Ser Leu Ala Trp Glu Glu Pro Leu Thr Asp Gly Gly Ser Lys Ile
        6610                6615                    6620
Ile Gly Tyr Val Val Glu Arg Arg Asp Ile Lys Arg Lys Thr Trp Val
6625                6630                    6635                6640
Leu Ala Thr Asp Arg Ala Glu Ser Cys Glu Phe Thr Val Thr Gly Leu
        6645                6650                    6655
Gln Lys Gly Gly Val Glu Tyr Leu Phe Arg Val Ser Ala Arg Asn Arg
        6660                6665                    6670
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Val Gly Thr Gly Glu Pro Val Glu Thr Asp Asn Pro Val Glu Ala Arg
        6675                6680                6685
Ser Lys Tyr Asp Val Pro Gly Pro Pro Leu Asn Val Thr Ile Thr Asp
        6690                6695                6700
Val Asn Arg Phe Gly Val Ser Leu Thr Trp Glu Pro Pro Glu Tyr Asp
6705                6710                6715                6720
Gly Gly Ala Glu Ile Thr Asn Tyr Val Ile Glu Leu Arg Asp Lys Thr
                6725                6730                6735
Ser Ile Arg Trp Asp Thr Ala Met Thr Val Arg Ala Glu Asp Leu Ser
        6740                6745                6750
Ala Thr Val Thr Asp Val Val Gly Gln Glu Tyr Ser Phe Arg Val
        6755                6760                6765
Arg Ala Gln Asn Arg Ile Gly Val Gly Lys Pro Ser Ala Ala Thr Pro
        6770                6775                6780
Phe Val Lys Val Ala Asp Pro Ile Glu Arg Pro Ser Pro Pro Val Asn
6785                6790                6795                6800
Leu Thr Ser Ser Asp Gln Thr Gln Ser Ser Val Gln Leu Lys Trp Glu
                6805                6810                6815
Pro Pro Leu Lys Asp Gly Gly Ser Pro Ile Leu Gly Tyr Ile Ile Glu
            6820                6825                6830
Arg Cys Glu Glu Gly Lys Asp Asn Trp Ile Arg Cys Asn Met Lys Leu
        6835                6840                6845
Val Pro Glu Leu Thr Tyr Lys Val Thr Gly Leu Glu Lys Gly Asn Lys
        6850                6855                6860
Tyr Leu Tyr Arg Val Ser Ala Glu Asn Lys Ala Gly Val Ser Asp Pro
6865                6870                6875                6880
Ser Glu Ile Leu Gly Pro Leu Thr Ala Asp Asp Ala Phe Val Glu Pro
                6885                6890                6895
Thr Met Asp Leu Ser Ala Phe Lys Asp Gly Leu Glu Val Ile Val Pro
            6900                6905                6910
Asn Pro Ile Thr Ile Leu Val Pro Ser Thr Gly Tyr Pro Arg Pro Thr
        6915                6920                6925
Ala Thr Trp Cys Phe Gly Asp Lys Val Leu Glu Thr Gly Asp Arg Val
        6930                6935                6940
Lys Met Lys Thr Leu Ser Ala Tyr Ala Glu Leu Val Ile Ser Pro Ser
6945                6950                6955                6960
Glu Arg Ser Asp Lys Gly Ile Tyr Thr Leu Lys Leu Glu Asn Arg Val
                6965                6970                6975
Lys Thr Ile Ser Gly Glu Ile Asp Val Asn Val Ile Ala Arg Pro Ser
            6980                6985                6990
Ala Pro Lys Glu Leu Lys Phe Gly Asp Ile Thr Lys Asp Ser Val His
        6995                7000                7005
Leu Thr Trp Glu Pro Pro Asp Asp Asp Gly Gly Ser Pro Leu Thr Gly
        7010                7015                7020
Tyr Val Val Glu Lys Arg Glu Val Ser Arg Lys Thr Trp Thr Lys Val
7025                7030                7035                7040
Met Asp Phe Val Thr Asp Leu Glu Phe Thr Val Pro Asp Leu Val Gln
                7045                7050                7055
Gly Lys Glu Tyr Leu Phe Lys Val Cys Ala Arg Asn Lys Cys Gly Pro
            7060                7065                7070
Gly Glu Pro Ala Tyr Val Asp Glu Pro Val Asn Met Ser Thr Pro Ala
        7075                7080                7085
Thr Val Pro Asp Pro Pro Glu Asn Val Lys Trp Arg Asp Arg Thr Ala
        7090                7095                7100
Asn Ser Ile Phe Leu Thr Trp Asp Pro Pro Lys Asn Asp Gly Gly Ser
7105                7110                7115                7120
Arg Ile Lys Gly Tyr Ile Val Glu Arg Cys Pro Arg Gly Ser Asp Lys
                7125                7130                7135
Trp Val Ala Cys Gly Glu Pro Val Ala Glu Thr Lys Met Glu Val Thr
            7140                7145                7150
Gly Leu Glu Glu Gly Lys Trp Tyr Ala Tyr Arg Val Lys Thr Leu Asn
        7155                7160                7165
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Arg Gln Gly Ala Ser Lys Pro Ser Arg Pro Thr Glu Glu Ile Gln Ala
    7170                7175                7180
Val Asp Thr Gln Glu Ala Pro Glu Ile Phe Leu Asp Val Lys Leu Leu
7185                7190                7195                7200
Ala Gly Leu Thr Val Lys Ala Gly Thr Lys Ile Glu Leu Pro Ala Thr
            7205                7210                7215
Val Thr Gly Lys Pro Glu Pro Lys Ile Thr Trp Thr Lys Ala Asp Met
        7220                7225                7230
Ile Leu Lys Gln Asp Lys Arg Ile Thr Ile Glu Asn Val Pro Lys Lys
        7235                7240                7245
Ser Thr Val Thr Ile Val Asp Ser Lys Arg Ser Asp Thr Gly Thr Tyr
    7250                7255                7260
Ile Ile Glu Ala Val Asn Val Cys Gly Arg Ala Thr Ala Val Val Glu
7265                7270                7275                7280
Val Asn Val Leu Asp Lys Pro Gly Pro Pro Ala Ala Phe Asp Ile Thr
            7285                7290                7295
Asp Val Thr Asn Glu Ser Cys Leu Leu Thr Trp Asn Pro Pro Arg Asp
        7300                7305                7310
Asp Gly Gly Ser Lys Ile Thr Asn Tyr Val Val Glu Arg Arg Ala Thr
    7315                7320                7325
Asp Ser Glu Val Trp His Lys Leu Ser Ser Thr Val Lys Asp Thr Asn
    7330                7335                7340
Phe Lys Ala Thr Lys Leu Ile Pro Asn Lys Glu Tyr Ile Phe Arg Val
7345                7350                7355                7360
Ala Ala Glu Asn Met Tyr Gly Ala Gly Glu Pro Val Gln Ala Ser Pro
            7365                7370                7375
Ile Thr Ala Lys Tyr Gln Phe Asp Pro Pro Gly Pro Pro Thr Arg Leu
        7380                7385                7390
Glu Pro Ser Asp Ile Thr Lys Asp Ala Val Thr Leu Thr Trp Cys Glu
    7395                7400                7405
Pro Asp Asp Asp Gly Gly Ser Pro Ile Thr Gly Tyr Trp Val Glu Arg
    7410                7415                7420
Leu Asp Pro Asp Thr Asp Lys Trp Val Arg Cys Asn Lys Met Pro Val
7425                7430                7435                7440
Lys Asp Thr Thr Tyr Arg Val Lys Gly Leu Thr Asn Lys Lys Lys Tyr
            7445                7450                7455
Arg Phe Arg Val Leu Ala Glu Asn Leu Ala Gly Pro Gly Lys Pro Ser
            7460                7465                7470
Lys Ser Thr Glu Pro Ile Leu Ile Lys Asp Pro Ile Asp Pro Pro Trp
    7475                7480                7485
Pro Pro Gly Lys Pro Thr Val Lys Asp Val Gly Lys Thr Ser Val Arg
    7490                7495                7500
Leu Asn Trp Thr Lys Pro Glu His Asp Gly Gly Ala Lys Ile Glu Ser
7505                7510                7515                7520
Tyr Val Ile Glu Met Leu Lys Thr Gly Thr Asp Glu Trp Val Arg Val
            7525                7530                7535
Ala Glu Gly Val Pro Thr Thr Gln His Leu Leu Pro Gly Leu Met Glu
            7540                7545                7550
Gly Gln Glu Tyr Ser Phe Arg Val Arg Ala Val Asn Lys Ala Gly Glu
    7555                7560                7565
Ser Glu Pro Ser Glu Pro Ser Asp Pro Val Leu Cys Arg Glu Lys Leu
    7570                7575                7580
Tyr Pro Pro Ser Pro Arg Trp Leu Glu Val Ile Asn Ile Thr Lys
7585                7590                7595                7600
Asn Thr Ala Asp Leu Lys Trp Thr Val Pro Glu Lys Asp Gly Gly Ser
            7605                7610                7615
Pro Ile Thr Asn Tyr Ile Val Glu Lys Arg Asp Val Arg Arg Lys Gly
            7620                7625                7630
Trp Gln Thr Val Asp Thr Thr Val Lys Asp Thr Lys Cys Thr Val Thr
    7635                7640                7645
Pro Leu Thr Glu Gly Ser Leu Tyr Val Phe Arg Val Ala Ala Glu Asn
    7650                7655                7660
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Ala Ile Gly Gln Ser Asp Tyr Thr Glu Ile Glu Asp Ser Val Leu Ala
7665               7670                7675                7680
Lys Asp Thr Phe Thr Thr Pro Gly Pro Pro Tyr Ala Leu Ala Val Val
                7685                7690                7695
Asp Val Thr Lys Arg His Val Asp Leu Lys Trp Glu Pro Pro Lys Asn
                7700                7705                7710
Asp Gly Gly Arg Pro Ile Gln Arg Tyr Val Ile Glu Lys Lys Glu Arg
            7715                7720                7725
Leu Gly Thr Arg Trp Val Lys Ala Gly Lys Thr Ala Gly Pro Asp Cys
        7730                7735                7740
Asn Phe Arg Val Thr Asp Val Ile Glu Gly Thr Glu Val Gln Phe Gln
7745                7750                7755                7760
Val Arg Ala Glu Asn Glu Ala Gly Val Gly His Pro Ser Glu Pro Thr
                7765                7770                7775
Glu Ile Leu Ser Ile Glu Asp Pro Thr Ser Pro Pro Ser Pro Pro Leu
            7780                7785                7790
Asp Leu His Val Thr Asp Ala Gly Arg Lys His Ile Ala Ile Ala Trp
        7795                7800                7805
Lys Pro Pro Glu Lys Asn Gly Gly Ser Pro Ile Ile Gly Tyr His Val
        7810                7815                7820
Glu Met Cys Pro Val Gly Thr Glu Lys Trp Met Arg Val Asn Ser Arg
7825                7830                7835                7840
Pro Ile Lys Asp Leu Lys Phe Lys Val Glu Glu Gly Val Val Pro Asp
                7845                7850                7855
Lys Glu Tyr Val Leu Arg Val Arg Ala Val Asn Ala Ile Gly Val Ser
            7860                7865                7870
Glu Pro Ser Glu Ile Ser Glu Asn Val Val Ala Lys Asp Pro Asp Cys
        7875                7880                7885
Lys Pro Thr Ile Asp Leu Glu Thr His Asp Ile Ile Val Ile Glu Gly
        7890                7895                7900
Glu Lys Leu Ser Ile Pro Val Pro Phe Arg Ala Val Pro Val Pro Thr
7905                7910                7915                7920
Val Ser Trp His Lys Asp Gly Lys Glu Val Lys Ala Ser Asp Arg Leu
                7925                7930                7935
Thr Met Lys Asn Asp His Ile Ser Ala His Leu Glu Val Pro Lys Ser
            7940                7945                7950
Val Arg Ala Asp Ala Gly Ile Tyr Thr Ile Thr Leu Glu Asn Lys Leu
        7955                7960                7965
Gly Ser Ala Thr Ala Ser Ile Asn Val Lys Val Ile Gly Leu Pro Gly
        7970                7975                7980
Pro Cys Lys Asp Ile Lys Ala Ser Asp Ile Thr Lys Ser Ser Cys Lys
7985                7990                7995                8000
Leu Thr Trp Glu Pro Pro Glu Phe Asp Gly Gly Thr Pro Ile Leu His
                8005                8010                8015
Tyr Val Leu Glu Arg Arg Glu Ala Gly Arg Arg Thr Tyr Ile Pro Val
            8020                8025                8030
Met Ser Gly Glu Asn Lys Leu Ser Trp Thr Val Lys Asp Leu Ile Pro
            8035                8040                8045
Asn Gly Glu Tyr Phe Phe Arg Val Lys Ala Val Asn Lys Val Gly Gly
        8050                8055                8060
Gly Glu Tyr Ile Glu Leu Lys Asn Pro Val Ile Ala Gln Asp Pro Lys
8065                8070                8075                8080
Gln Pro Pro Asp Pro Pro Val Asp Val Glu Val His Asn Pro Thr Ala
                8085                8090                8095
Glu Ala Met Thr Ile Thr Trp Lys Pro Pro Leu Tyr Asp Gly Gly Ser
            8100                8105                8110
Lys Ile Met Gly Tyr Ile Ile Glu Lys Ile Ala Lys Gly Glu Glu Arg
        8115                8120                8125
Trp Lys Arg Cys Asn Glu His Leu Val Pro Ile Leu Thr Tyr Thr Ala
    8130                8135                8140
Lys Gly Leu Glu Glu Gly Lys Glu Tyr Gln Phe Arg Val Arg Ala Glu
8145                8150                8155                8160
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Asn Ala Ala Gly Ile Ser Glu Pro Ser Arg Ala Thr Pro Pro Thr Lys
            8165                    8170                    8175
Ala Val Asp Pro Ile Asp Ala Pro Lys Val Ile Leu Arg Thr Ser Leu
            8180                    8185                    8190
Glu Val Lys Arg Gly Asp Glu Ile Ala Leu Asp Ala Ser Ile Ser Gly
            8195                    8200                    8205
Ser Pro Tyr Pro Thr Ile Thr Trp Ile Lys Asp Glu Asn Val Ile Val
    8210                    8215                    8220
Pro Glu Glu Ile Lys Lys Arg Ala Ala Pro Leu Val Arg Arg Arg Lys
8225                    8230                    8235                    8240
Gly Glu Val Gln Glu Glu Glu Pro Phe Val Leu Pro Leu Thr Gln Arg
                8245                    8250                    8255
Leu Ser Ile Asp Asn Ser Lys Lys Gly Glu Ser Gln Leu Arg Val Arg
            8260                    8265                    8270
Asp Ser Leu Arg Pro Asp His Gly Leu Tyr Met Ile Lys Val Glu Asn
            8275                    8280                    8285
Asp His Gly Ile Ala Lys Ala Pro Cys Thr Val Ser Val Leu Asp Thr
    8290                    8295                    8300
Pro Gly Pro Pro Ile Asn Phe Val Phe Glu Asp Ile Arg Lys Thr Ser
8305                    8310                    8315                    8320
Val Leu Cys Lys Trp Glu Pro Pro Leu Asp Asp Gly Gly Ser Glu Ile
            8325                    8330                    8335
Ile Asn Tyr Thr Leu Glu Lys Lys Asp Lys Thr Lys Pro Asp Ser Glu
            8340                    8345                    8350
Trp Ile Val Val Thr Ser Thr Leu Arg His Cys Lys Tyr Ser Val Thr
    8355                    8360                    8365
Lys Leu Ile Glu Gly Lys Glu Tyr Leu Phe Arg Val Arg Ala Glu Asn
    8370                    8375                    8380
Arg Phe Gly Pro Gly Pro Pro Cys Val Ser Lys Pro Leu Val Ala Lys
8385                    8390                    8395                    8400
Asp Pro Phe Gly Pro Pro Asp Ala Pro Asp Lys Pro Ile Val Glu Asp
            8405                    8410                    8415
Val Thr Ser Asn Ser Met Leu Val Lys Trp Asn Glu Pro Lys Asp Asn
            8420                    8425                    8430
Gly Ser Pro Ile Leu Gly Tyr Trp Leu Glu Lys Arg Glu Val Asn Ser
            8435                    8440                    8445
Thr His Trp Ser Arg Val Asn Lys Ser Leu Leu Asn Ala Leu Lys Ala
    8450                    8455                    8460
Asn Val Asp Gly Leu Leu Glu Gly Leu Thr Tyr Val Phe Arg Val Cys
8465                    8470                    8475                    8480
Ala Glu Asn Ala Ala Gly Pro Gly Lys Phe Ser Pro Pro Ser Asp Pro
            8485                    8490                    8495
Lys Thr Ala His Asp Pro Ile Ser Pro Pro Gly Pro Pro Ile Pro Arg
    8500                    8505                    8510
Val Thr Asp Thr Ser Ser Thr Thr Ile Glu Leu Glu Trp Glu Pro Pro
    8515                    8520                    8525
Ala Phe Asn Gly Gly Gly Glu Ile Val Gly Tyr Phe Val Asp Lys Gln
    8530                    8535                    8540
Leu Val Gly Thr Asn Lys Trp Ser Arg Cys Thr Glu Lys Met Ile Lys
8545                    8550                    8555                    8560
Val Arg Gln Tyr Thr Val Lys Glu Ile Arg Glu Gly Ala Asp Tyr Lys
            8565                    8570                    8575
Leu Arg Val Ser Ala Val Asn Ala Ala Gly Glu Gly Pro Pro Gly Glu
            8580                    8585                    8590
Thr Gln Pro Val Thr Val Ala Glu Pro Gln Glu Pro Pro Ala Val Glu
    8595                    8600                    8605
Leu Asp Val Ser Val Lys Gly Gly Ile Gln Ile Met Ala Gly Lys Thr
    8610                    8615                    8620
Leu Arg Ile Pro Ala Val Val Thr Gly Arg Pro Val Pro Thr Lys Val
8625                    8630                    8635                    8640
Trp Thr Lys Glu Glu Gly Glu Leu Asp Lys Asp Arg Val Val Ile Asp
            8645                    8650                    8655
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Asn Val Gly Thr Lys Ser Glu Leu Ile Ile Lys Asp Ala Leu Arg Lys
         8660                8665                8670
Asp His Gly Arg Tyr Val Ile Thr Ala Thr Asn Ser Cys Gly Ser Lys
         8675                8680                8685
Phe Ala Ala Ala Arg Val Glu Val Phe Asp Val Pro Gly Pro Val Leu
     8690                8695                8700
Asp Leu Lys Pro Val Val Thr Asn Arg Lys Met Cys Leu Leu Asn Trp
8705                8710                8715                8720
Ser Asp Pro Glu Asp Asp Gly Gly Ser Glu Ile Thr Gly Phe Ile Ile
         8725                8730                8735
Glu Arg Lys Asp Ala Lys Met His Thr Trp Arg Gln Pro Ile Glu Thr
         8740                8745                8750
Glu Arg Ser Lys Cys Asp Ile Thr Gly Leu Leu Glu Gly Gln Glu Tyr
     8755                8760                8765
Lys Phe Arg Val Ile Ala Lys Asn Lys Phe Gly Cys Gly Pro Pro Val
     8770                8775                8780
Glu Ile Gly Pro Ile Leu Ala Val Asp Pro Leu Gly Pro Pro Thr Ser
8785                8790                8795                8800
Pro Glu Arg Leu Thr Tyr Thr Glu Arg Gln Arg Ser Thr Ile Thr Leu
         8805                8810                8815
Asp Trp Lys Glu Pro Arg Ser Asn Gly Gly Ser Pro Ile Gln Gly Tyr
         8820                8825                8830
Ile Ile Glu Lys Arg Arg His Asp Lys Pro Asp Phe Glu Arg Val Asn
     8835                8840                8845
Lys Arg Leu Cys Pro Thr Thr Ser Phe Leu Val Glu Asn Leu Asp Glu
     8850                8855                8860
His Gln Met Tyr Glu Phe Arg Val Lys Ala Val Asn Glu Ile Gly Glu
8865                8870                8875                8880
Ser Glu Pro Ser Leu Pro Leu Asn Val Val Ile Gln Asp Asp Glu Val
         8885                8890                8895
Pro Pro Thr Ile Lys Leu Arg Leu Ser Val Arg Gly Asp Thr Ile Lys
         8900                8905                8910
Val Lys Ala Gly Glu Pro Val His Ile Pro Ala Asp Val Thr Gly Leu
     8915                8920                8925
Pro Met Pro Lys Ile Glu Trp Ser Lys Asn Glu Thr Val Ile Glu Lys
     8930                8935                8940
Pro Thr Asp Ala Leu Gln Ile Thr Lys Glu Glu Val Ser Arg Ser Glu
8945                8950                8955                8960
Ala Lys Thr Glu Leu Ser Ile Pro Lys Ala Val Arg Glu Asp Lys Gly
         8965                8970                8975
Thr Tyr Thr Val Thr Ala Ser Asn Arg Leu Gly Ser Val Phe Arg Asn
         8980                8985                8990
Val His Val Glu Val Tyr Asp Arg Pro Ser Pro Pro Arg Asn Leu Ala
     8995                9000                9005
Val Thr Asp Ile Lys Ala Glu Ser Cys Tyr Leu Thr Trp Asp Ala Pro
     9010                9015                9020
Leu Asp Asn Gly Gly Ser Glu Ile Thr His Tyr Val Ile Asp Lys Arg
9025                9030                9035                9040
Asp Ala Ser Arg Lys Lys Ala Glu Trp Glu Glu Val Thr Asn Thr Ala
         9045                9050                9055
Val Glu Lys Arg Tyr Gly Ile Trp Lys Leu Ile Pro Asn Gly Gln Tyr
         9060                9065                9070
Glu Phe Arg Val Arg Ala Val Asn Lys Tyr Gly Ile Ser Asp Glu Cys
         9075                9080                9085
Lys Ser Asp Lys Val Val Ile Gln Asp Pro Tyr Arg Leu Pro Gly Pro
     9090                9095                9100
Pro Gly Lys Pro Lys Val Leu Ala Arg Thr Lys Gly Ser Met Leu Val
9105                9110                9115                9120
Ser Trp Thr Pro Pro Leu Asp Asn Gly Gly Ser Pro Ile Thr Gly Tyr
         9125                9130                9135
Trp Leu Glu Lys Arg Glu Glu Gly Ser Pro Tyr Trp Ser Arg Val Ser
         9140                9145                9150
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Arg Ala Pro Ile Thr Lys Val Gly Leu Lys Gly Val Glu Phe Asn Val
        9155                9160                9165
Pro Arg Leu Leu Glu Gly Val Lys Tyr Gln Phe Arg Ala Met Ala Ile
        9170                9175                9180
Asn Ala Ala Gly Ile Gly Pro Pro Ser Glu Pro Ser Asp Pro Glu Val
9185                9190                9195                9200
Ala Gly Asp Pro Ile Phe Pro Pro Gly Pro Pro Ser Cys Pro Glu Val
        9205                9210                9215
Lys Asp Lys Thr Lys Ser Ser Ile Ser Leu Gly Trp Lys Pro Pro Ala
        9220                9225                9230
Lys Asp Gly Gly Ser Pro Ile Lys Gly Tyr Ile Val Glu Met Gln Glu
        9235                9240                9245
Glu Gly Thr Thr Asp Trp Lys Arg Val Asn Glu Pro Asp Lys Leu Ile
    9250                9255                9260
Thr Thr Cys Glu Cys Val Val Pro Asn Leu Lys Glu Leu Arg Lys Tyr
9265                9270                9275                9280
Arg Phe Arg Val Lys Ala Val Asn Glu Ala Gly Glu Ser Glu Pro Ser
        9285                9290                9295
Asp Thr Thr Gly Glu Ile Pro Ala Thr Asp Ile Gln Glu Glu Pro Glu
        9300                9305                9310
Val Phe Ile Asp Ile Gly Ala Gln Asp Cys Leu Val Cys Lys Ala Gly
        9315                9320                9325
Ser Gln Ile Arg Ile Pro Ala Val Ile Lys Gly Arg Pro Thr Pro Lys
    9330                9335                9340
Ser Ser Trp Glu Phe Asp Gly Lys Ala Lys Lys Ala Met Lys Asp Gly
9345                9350                9355                9360
Val His Asp Ile Pro Glu Asp Ala Gln Leu Glu Thr Ala Glu Asn Ser
        9365                9370                9375
Ser Val Ile Ile Ile Pro Glu Cys Lys Arg Ser His Thr Gly Lys Tyr
        9380                9385                9390
Ser Ile Thr Ala Lys Asn Lys Ala Gly Gln Lys Thr Ala Asn Cys Arg
    9395                9400                9405
Val Lys Val Met Asp Val Pro Gly Pro Pro Lys Asp Leu Lys Val Ser
    9410                9415                9420
Asp Ile Thr Arg Gly Ser Cys Arg Leu Ser Trp Lys Met Pro Asp Asp
9425                9430                9435                9440
Asp Gly Gly Asp Arg Ile Lys Gly Tyr Val Ile Glu Lys Arg Thr Ile
        9445                9450                9455
Asp Gly Lys Ala Trp Thr Lys Val Asn Pro Asp Cys Gly Ser Thr Thr
        9460                9465                9470
Phe Val Val Pro Asp Leu Leu Ser Glu Gln Gln Tyr Phe Phe Arg Val
        9475                9480                9485
Arg Ala Glu Asn Arg Phe Gly Ile Gly Pro Pro Val Glu Thr Ile Gln
    9490                9495                9500
Arg Thr Thr Ala Arg Asp Pro Ile Tyr Pro Pro Asp Pro Pro Ile Lys
9505                9510                9515                9520
Leu Lys Ile Gly Leu Ile Thr Lys Asn Thr Val His Leu Ser Trp Lys
        9525                9530                9535
Pro Pro Lys Asn Asp Gly Gly Ser Pro Val Thr His Tyr Ile Val Glu
        9540                9545                9550
Cys Leu Ala Trp Asp Pro Thr Gly Thr Lys Lys Glu Ala Trp Arg Gln
        9555                9560                9565
Cys Asn Lys Arg Asp Val Glu Glu Leu Gln Phe Thr Val Glu Asp Leu
9570                9575                9580
Val Glu Gly Gly Glu Tyr Glu Phe Arg Val Lys Ala Val Asn Ala Ala
9585                9590                9595                9600
Gly Val Ser Lys Pro Ser Ala Thr Val Gly Pro Cys Asp Cys Gln Arg
        9605                ·9610               9615
Pro Asp Met Pro Pro Ser Ile Asp Leu Lys Glu Phe Met Glu Val Glu
        9620                9625                9630
Glu Gly Thr Asn Val Asn Ile Val Ala Lys Ile Lys Gly Val Pro Phe
    9635                9640                9645
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Pro Thr Leu Thr Trp Phe Lys Ala Pro Pro Lys Lys Pro Asp Asn Lys
    9650                9655                9660
Glu Pro Val Leu Tyr Asp Thr His Val Asn Lys Leu Val Val Asp Asp
9665                9670                9675                9680
Thr Cys Thr Leu Val Ile Pro Gln Ser Arg Arg Ser Asp Thr Gly Leu
                9685                9690                9695
Tyr Thr Ile Thr Ala Val Asn Asn Leu Gly Thr Ala Ser Lys Glu Met
            9700                9705                9710
Arg Leu Asn Val Leu Gly Arg Pro Gly Pro Pro Val Gly Pro Ile Lys
        9715                9720                9725
Phe Glu Ser Val Ser Ala Asp Gln Met Thr Leu Ser Trp Phe Pro Pro
    9730                9735                9740
Lys Asp Asp Gly Gly Ser Lys Ile Thr Asn Tyr Val Ile Glu Lys Arg
9745                9750                9755                9760
Glu Ala Asn Arg Lys Thr Trp Val His Val Ser Ser Glu Pro Lys Glu
                9765                9770                9775
Cys Thr Tyr Thr Ile Pro Lys Leu Leu Glu Gly His Glu Tyr Val Phe
            9780                9785                9790
Arg Ile Met Ala Gln Asn Lys Tyr Gly Ile Gly Glu Pro Leu Asp Ser
        9795                9800                9805
Glu Pro Glu Thr Ala Arg Asn Leu Phe Ser Val Pro Gly Ala Pro Asp
    9810                9815                9820
Lys Pro Thr Val Ser Ser Val Thr Arg Asn Ser Met Thr Val Asn Trp
9825                9830                9835                9840
Glu Glu Pro Glu Tyr Asp Gly Gly Ser Pro Val Thr Gly Tyr Trp Leu
                9845                9850                9855
Glu Met Lys Asp Thr Thr Ser Lys Arg Trp Lys Arg Val Asn Arg Asp
            9860                9865                9870
Pro Ile Lys Ala Met Thr Leu Gly Val Ser Tyr Lys Val Thr Gly Leu
            9875                9880                9885
Ile Glu Gly Ser Asp Tyr Gln Phe Arg Val Tyr Ala Ile Asn Ala Ala
    9890                9895                9900
Gly Val Gly Pro Ala Ser Leu Pro Ser Asp Pro Ala Thr Ala Arg Asp
9905                9910                9915                9920
Pro Ile Ala Pro Pro Gly Pro Pro Phe Pro Lys Val Thr Asp Trp Thr
            9925                9930                9935
Lys Ser Ser Ala Asp Leu Glu Trp Ser Pro Pro Leu Lys Asp Gly Gly
        9940                9945                9950
Ser Lys Val Thr Gly Tyr Ile Val Glu Tyr Lys Glu Glu Gly Lys Glu
        9955                9960                9965
Glu Trp Glu Lys Gly Lys Asp Lys Glu Val Arg Gly Thr Lys Leu Val
    9970                9975                9980
Val Thr Gly Leu Lys Glu Gly Ala Phe Tyr Lys Phe Arg Val Ser Ala
9985                9990                9995                10000
Val Asn Ile Ala Gly Ile Gly Glu Pro Gly Glu Val Thr Asp Val Ile
            10005               10010               10015
Glu Met Lys Asp Arg Leu Val Ser Pro Asp Leu Gln Leu Asp Ala Ser
        10020               10025               10030
Val Arg Asp Arg Ile Val Val His Ala Gly Gly Val Ile Arg Ile Ile
        10035               10040               10045
Ala Tyr Val Ser Gly Lys Pro Pro Pro Thr Val Thr Trp Asn Met Asn
    10050               10055               10060                1
Glu Arg Thr Leu Pro Gln Glu Ala Thr Ile Glu Thr Thr Ala Ile Ser
0065                10070               10075               10080
Ser Ser Met Val Ile Lys Asn Cys Gln Arg Ser His Gln Gly Val Tyr
                10085               10090               10095
Ser Leu Leu Ala Lys Asn Glu Ala Gly Glu Arg Lys Lys Thr Ile Ile
        10100               10105               10110
Val Asp Val Leu Asp Val Pro Gly Pro Val Gly Thr Pro Phe Leu Ala
    10115               10120               10125
His Asn Leu Thr Asn Glu Ser Cys Lys Leu Thr Trp Phe Ser Pro Glu
    10130               10135               10140                1
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Asp Asp Gly Gly Ser Pro Ile Thr Asn Tyr Val Ile Glu Lys Arg Glu
0145            10150               10155               10160
Ser Asp Arg Arg Ala Trp Thr Pro Val Thr Tyr Thr Val Thr Arg Gln
                10165               10170               10175
Asn Ala Thr Val Gln Gly Leu Ile Gln Gly Lys Ala Tyr Phe Phe Arg
                10180               10185           10190
Ile Ala Ala Glu Asn Ser Ile Gly Met Gly Pro Phe Val Glu Thr Ser
        10195               10200               10205
Glu Ala Leu Val Ile Arg Glu Pro Ile Thr Val Pro Glu Arg Pro Glu
    10210               10215               10220           1
Asp Leu Glu Val Lys Glu Val Thr Lys Asn Thr Val Thr Leu Thr Trp
0225            10230               10235               10240
Asn Pro Pro Lys Tyr Asp Gly Gly Ser Glu Ile Ile Asn Tyr Val Leu
                10245               10250               10255
Glu Ser Arg Leu Ile Gly Thr Glu Lys Phe His Lys Val Thr Asn Asp
            10260               10265               10270
Asn Leu Leu Ser Arg Lys Tyr Thr Val Lys Gly Leu Lys Glu Gly Asp
            10275               10280               10285
Thr Tyr Glu Tyr Arg Val Ser Ala Val Asn Ile Val Gly Gln Gly Lys
        10290               10295               10300           1
Pro Ser Phe Cys Thr Lys Pro Ile Thr Cys Lys Asp Glu Leu Ala Pro
0305            10310               10315               10320
Pro Thr Leu His Leu Asp Phe Arg Asp Lys Leu Thr Ile Arg Val Gly
                10325               10330               10335
Glu Ala Phe Ala Leu Thr Gly Arg Tyr Ser Gly Lys Pro Lys Pro Lys
            10340               10345               10350
Val Ser Trp Phe Lys Asp Glu Ala Asp Val Leu Glu Asp Asp Arg Thr
        10355               10360               10365
His Ile Lys Thr Thr Pro Ala Thr Leu Ala Leu Glu Lys Ile Lys Ala
    10370               10375               10380           1
Lys Arg Ser Asp Ser Gly Lys Tyr Cys Val Val Val Glu Asn Ser Thr
0385            10390               10395               10400
Gly Ser Arg Lys Gly Phe Cys Gln Val Asn Val Val Asp His Pro Gly
            10405               10410               10415
Pro Pro Val Gly Pro Val Ser Phe Asp Glu Val Thr Lys Asp Tyr Met
        10420               10425               10430
Val Ile Ser Trp Lys Pro Pro Leu Asp Asp Gly Gly Ser Lys Ile Thr
        10435               10440               10445
Asn Tyr Ile Ile Glu Lys Lys Glu Val Gly Lys Asp Val Trp Met Pro
    10450               10455               10460           1
Val Thr Ser Ala Ser Ala Lys Thr Thr Cys Lys Val Ser Lys Leu Leu
0465            10470               10475               10480
Glu Gly Lys Asp Tyr Ile Phe Arg Ile His Ala Glu Asn Leu Tyr Gly
            10485               10490               10495
Ile Ser Asp Pro Leu Val Ser Asp Ser Met Lys Ala Lys Asp Arg Phe
        10500               10505               10510
Arg Val Pro Asp Ala Pro Asp Gln Pro Ile Val Thr Glu Val Thr Lys
        10515               10520               10525
Asp Ser Ala Leu Val Thr Trp Asn Lys Pro His Asp Gly Gly Lys Pro
    10530               10535               10540           1
Ile Thr Asn Tyr Ile Leu Glu Lys Arg Glu Thr Met Ser Lys Arg Trp
0545            10550               10555               10560
Ala Arg Val Thr Lys Asp Pro Ile His Pro Tyr Thr Lys Phe Arg Val
                10565               10570               10575
Pro Asp Leu Leu Glu Gly Cys Gln Tyr Glu Phe Arg Val Ser Ala Glu
            10580               10585               10590
Asn Glu Ile Gly Ile Gly Asp Pro Ser Pro Pro Ser Lys Pro Val Phe
        10595               10600               10605
Ala Lys Asp Pro Ile Ala Lys Pro Ser Pro Pro Val Asn Pro Glu Ala
    10610               10615               10620           1
Ile Asp Thr Thr Cys Asn Ser Val Asp Leu Thr Trp Gln Pro Pro Arg
0625            10630               10635               10640
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His Asp Gly Gly Ser Lys Ile Leu Gly Tyr Ile Val Glu Tyr Gln Lys
          10645                10650                10655
Val Gly Asp Glu Glu Trp Arg Arg Ala Asn His Thr Pro Glu Ser Cys
          10660                10665                10670
Pro Glu Thr Lys Tyr Lys Val Thr Gly Leu Arg Asp Gly Gln Thr Tyr
          10675                10680                10685
Lys Phe Arg Val Leu Ala Val Asn Ala Ala Gly Glu Ser Asp Pro Ala
       10690                10695                10700                1
His Val Pro Glu Pro Val Leu Val Lys Asp Arg Leu Glu Pro Pro Glu
0705                10710                10715                10720
Leu Ile Leu Asp Ala Asn Met Ala Arg Gln His Ile Lys Val Gly
          10725                10730                10735
Asp Thr Leu Arg Leu Ser Ala Ile Ile Lys Gly Val Pro Phe Pro Lys
          10740                10745                10750
Val Thr Trp Lys Lys Glu Asp Arg Asp Ala Pro Thr Lys Ala Arg Ile
       10755                10760                10765
Asp Val Thr Pro Val Gly Ser Lys Leu Glu Ile Arg Asn Ala Ala His
    10770                10775                10780                1
Glu Asp Gly Gly Ile Tyr Ser Leu Thr Val Glu Asn Pro Ala Gly Ser
0785                10790                10795                10800
Lys Thr Val Ser Val Lys Val Leu Val Leu Asp Lys Pro Gly Pro Pro
          10805                10810                10815
Arg Asp Leu Glu Val Ser Glu Ile Arg Lys Asp Ser Cys Tyr Leu Thr
       10820                10825                10830
Trp Lys Glu Pro Leu Asp Asp Gly Gly Ser Val Ile Thr Asn Tyr Val
       10835                10840                10845
Val Glu Arg Arg Asp Val Ala Ser Ala Gln Trp Ser Pro Leu Ser Ala
    10850                10855                10860                1
Thr Ser Lys Lys Lys Ser His Phe Ala Lys His Leu Asn Glu Gly Asn
0865                10870                10875                10880
Gln Tyr Leu Phe Arg Val Ala Ala Glu Asn Gln Tyr Gly Arg Gly Pro
          10885                10890                10895
Phe Val Glu Thr Pro Lys Pro Ile Lys Ala Leu Asp Pro Leu His Pro
       10900                10905                10910
Pro Gly Pro Pro Lys Asp Leu His His Val Asp Val Asp Lys Thr Glu
       10915                10920                10925
Val Ser Leu Val Trp Asn Lys Pro Asp Arg Asp Gly Gly Ser Pro Ile
    10930                10935                10940                1
Thr Gly Tyr Leu Val Glu Tyr Gln Glu Glu Gly Thr Gln Asp Trp Ile
0945                10950                10955                10960
Lys Phe Lys Thr Val Thr Asn Leu Glu Cys Val Val Thr Gly Leu Gln
          10965                10970                10975
Gln Gly Lys Thr Tyr Arg Phe Arg Val Lys Ala Glu Asn Ile Val Gly
       10980                10985                10990
Leu Gly Leu Pro Asp Thr Thr Ile Pro Ile Glu Cys Gln Glu Lys Leu
       10995                11000                11005
Val Pro Pro Ser Val Glu Leu Asp Val Lys Leu Ile Glu Gly Leu Val
    11010                11015                11020                1
Val Lys Ala Gly Thr Thr Val Arg Phe Pro Ala Ile Ile Arg Gly Val
1025                11030                11035                11040
Pro Val Pro Thr Ala Lys Trp Thr Thr Asp Gly Ser Glu Ile Lys Thr
          11045                11050                11055
Asp Glu His Tyr Thr Val Glu Thr Asp Asn Phe Ser Ser Val Leu Thr
       11060                11065                11070
Ile Lys Asn Cys Leu Arg Arg Asp Thr Gly Glu Tyr Gln Ile Thr Val
    11075                11080                11085
Ser Asn Ala Ala Gly Ser Lys Thr Val Ala Val His Leu Thr Val Leu
    11090                11095                11100                1
Asp Val Pro Gly Pro Pro Thr Gly Pro Ile Asn Ile Leu Asp Val Thr
1105                11110                11115                11120
Pro Glu His Met Thr Ile Ser Trp Gln Pro Pro Lys Asp Asp Gly Gly
          11125                11130                11135
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Ser Pro Val Ile Asn Tyr Ile Val Glu Lys Gln Asp Thr Arg Lys Asp
        11140                11145                11150
Thr Trp Gly Val Val Ser Ser Gly Ser Ser Lys Thr Lys Leu Lys Ile
        11155                11160                11165
Pro His Leu Gln Lys Gly Cys Glu Tyr Val Phe Arg Val Arg Ala Glu
      11170                11175                11180             1
Asn Lys Ile Gly Val Gly Pro Pro Leu Asp Ser Thr Pro Thr Val Ala
1185            11190                11195                11200
Lys His Lys Phe Ser Pro Pro Ser Pro Pro Gly Lys Pro Val Val Thr
              11205                11210                11215
Asp Ile Thr Glu Asn Ala Ala Thr Val Ser Trp Thr Leu Pro Lys Ser
          11220                11225                11230
Asp Gly Gly Ser Pro Ile Thr Gly Tyr Tyr Met Glu Arg Arg Glu Val
        11235                11240                11245
Thr Gly Lys Trp Val Arg Val Asn Lys Thr Pro Ile Ala Asp Leu Lys
      11250                11255                11260             1
Phe Arg Val Thr Gly Leu Tyr Glu Gly Asn Thr Tyr Glu Phe Arg Val
1265            11270                11275                11280
Phe Ala Glu Asn Leu Ala Gly Leu Ser Lys Pro Ser Pro Ser Ser Asp
              11285                11290                11295
Pro Ile Lys Ala Cys Arg Pro Ile Lys Pro Pro Gly Pro Pro Ile Asn
        11300                11305                11310
Pro Lys Leu Lys Asp Lys Ser Arg Glu Thr Ala Asp Leu Val Trp Thr
      11315                11320                11325
Lys Pro Leu Ser Asp Gly Gly Ser Pro Ile Leu Gly Tyr Val Val Glu
    11330                11335                11340               1
Cys Gln Lys Pro Gly Thr Ala Gln Trp Asn Arg Ile Asn Lys Asp Glu
1345            11350                11355                11360
Leu Ile Arg Gln Cys Ala Phe Arg Val Pro Gly Leu Ile Glu Gly Asn
              11365                11370                11375
Glu Tyr Arg Phe Arg Ile Lys Ala Ala Asn Ile Val Gly Glu Gly Glu
        11380                11385                11390
Pro Arg Glu Leu Ala Glu Ser Val Ile Ala Lys Asp Ile Leu His Pro
      11395                11400                11405
Pro Glu Val Glu Leu Asp Val Thr Cys Arg Asp Val Ile Thr Val Arg
    11410                11415                11420               1
Val Gly Gln Thr Ile Arg Ile Leu Ala Arg Val Lys Gly Arg Pro Glu
1425            11430                11435                11440
Pro Asp Ile Thr Trp Thr Lys Glu Gly Lys Val Leu Val Arg Glu Lys
              11445                11450                11455
Arg Val Asp Leu Ile Gln Asp Leu Pro Arg Val Glu Leu Gln Ile Lys
        11460                11465                11470
Glu Ala Val Arg Ala Asp His Gly Lys Tyr Ile Ile Ser Ala Lys Asn
      11475                11480                11485
Ser Ser Gly His Ala Gln Gly Ser Ala Ile Val Asn Val Leu Asp Arg
    11490                11495                11500               1
Pro Gly Pro Cys Gln Asn Leu Lys Val Thr Asn Val Thr Lys Glu Asn
1505            11510                11515                11520
Cys Thr Ile Ser Trp Glu Asn Pro Leu Asp Asn Gly Gly Ser Glu Ile
              11525                11530                11535
Thr Asn Phe Ile Val Glu Tyr Arg Lys Pro Asn Gln Lys Gly Trp Ser
          11540                11545                11550
Ile Val Ala Ser Asp Val Thr Lys Arg Leu Ile Lys Ala Asn Leu Leu
      11555                11560                11565
Ala Asn Asn Glu Tyr Tyr Phe Arg Val Cys Ala Glu Asn Lys Val Gly
    11570                11575                11580               1
Val Gly Pro Thr Ile Glu Thr Lys Thr Pro Ile Leu Ala Ile Asn Pro
1585            11590                11595                11600
Ile Asp Arg Pro Gly Glu Pro Glu Asn Leu His Ile Ala Asp Lys Gly
              11605                11610                11615
Lys Thr Phe Val Tyr Leu Lys Trp Arg Arg Pro Asp Tyr Asp Gly Gly
        11620                11625                11630
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Ser Pro Asn Leu Ser Tyr His Val Glu Arg Arg Leu Lys Gly Ser Asp
     11635               11640                11645
Asp Trp Glu Arg Val His Lys Gly Ser Ile Lys Glu Thr His Tyr Met
     11650               11655               11660                1
Val Asp Arg Cys Val Glu Asn Gln Ile Tyr Glu Phe Arg Val Gln Thr
  1665               11670               11675               11680
Lys Asn Glu Gly Gly Glu Ser Asp Trp Val Lys Thr Glu Glu Val Val
                11685               11690               11695
Val Lys Glu Asp Leu Gln Lys Pro Val Leu Asp Leu Lys Leu Ser Gly
     11700               11705               11710
Val Leu Thr Val Lys Ala Gly Asp Thr Ile Arg Leu Glu Ala Gly Val
     11715               11720               11725
Arg Gly Lys Pro Phe Pro Glu Val Ala Trp Thr Lys Asp Lys Asp Ala
     11730               11735               11740                1
Thr Asp Leu Thr Arg Ser Pro Arg Val Lys Ile Asp Thr Arg Ala Asp
  1745               11750               11755               11760
Ser Ser Lys Phe Ser Leu Thr Lys Ala Lys Arg Ser Asp Gly Gly Lys
                11765               11770               11775
Tyr Val Val Thr Ala Thr Asn Thr Ala Gly Ser Phe Val Ala Tyr Ala
                11780               11785               11790
Thr Val Asn Val Leu Asp Lys Pro Gly Pro Val Arg Asn Leu Lys Ile
     11795               11800               11805
Val Asp Val Ser Ser Asp Arg Cys Thr Val Cys Trp Asp Pro Pro Glu
     11810               11815               11820                1
Asp Asp Gly Gly Cys Glu Ile Gln Asn Tyr Ile Leu Glu Lys Cys Glu
  1825               11830               11835               11840
Thr Lys Arg Met Val Trp Ser Thr Tyr Ser Ala Thr Val Leu Thr Pro
                11845               11850               11855
Gly Thr Thr Val Thr Arg Leu Ile Glu Gly Asn Glu Tyr Ile Phe Arg
                11860               11865               11870
Val Arg Ala Glu Asn Lys Ile Gly Thr Gly Pro Pro Thr Glu Ser Lys
     11875               11880               11885
Pro Val Ile Ala Lys Thr Lys Tyr Asp Lys Pro Gly Arg Pro Asp Pro
     11890               11895               11900                1
Pro Glu Val Thr Lys Val Ser Lys Glu Glu Met Thr Val Val Trp Asn
  1905               11910               11915               11920
Pro Pro Glu Tyr Asp Gly Gly Lys Ser Ile Thr Gly Tyr Phe Leu Glu
                11925               11930               11935
Lys Lys Glu Lys His Ser Thr Arg Trp Val Pro Val Asn Lys Ser Ala
                11940               11945               11950
Ile Pro Glu Arg Arg Met Lys Val Gln Asn Leu Leu Pro Asp His Glu
     11955               11960               11965
Tyr Gln Phe Arg Val Lys Ala Glu Asn Glu Ile Gly Ile Gly Glu Pro
     11970               11975               11980                1
Ser Leu Pro Ser Arg Pro Val Val Ala Lys Asp Pro Ile Glu Pro Pro
  1985               11990               11995               12000
Gly Pro Pro Thr Asn Phe Arg Val Val Asp Thr Thr Lys His Ser Ile
                12005               12010               12015
Thr Leu Gly Trp Gly Lys Pro Val Tyr Asp Gly Gly Ala Pro Ile Ile
                12020               12025               12030
Gly Tyr Val Val Glu Met Arg Pro Lys Ile Ala Asp Ala Ser Pro Asp
     12035               12040               12045
Glu Gly Trp Lys Arg Cys Asn Ala Ala Ala Gln Leu Val Arg Lys Glu
     12050               12055               12060                1
Phe Thr Val Thr Ser Leu Asp Glu Asn Gln Glu Tyr Glu Phe Arg Val
  2065               12070               12075               12080
Cys Ala Gln Asn Gln Val Gly Ile Gly Arg Pro Ala Glu Leu Lys Glu
                12085               12090               12095
Ala Ile Lys Pro Lys Glu Ile Leu Glu Pro Pro Glu Ile Asp Leu Asp
     12100               12105               12110
Ala Ser Met Arg Lys Leu Val Ile Val Arg Ala Gly Cys Pro Ile Arg
     12115               12120               12125
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Leu Phe Ala Ile Val Arg Gly Arg Pro Ala Pro Lys Val Thr Trp Arg
    12130           12135           12140                   1
Lys Val Gly Ile Asp Asn Val Val Arg Lys Gly Gln Val Asp Leu Val
2145            12150           12155                   12160
Asp Thr Met Ala Phe Leu Val Ile Pro Asn Ser Thr Arg Asp Asp Ser
            12165           12170           12175
Gly Lys Tyr Ser Leu Thr Leu Val Asn Pro Ala Gly Glu Lys Ala Val
            12180           12185           12190
Phe Val Asn Val Arg Val Leu Asp Thr Pro Gly Pro Val Ser Asp Leu
        12195           12200           12205
Lys Val Ser Asp Val Thr Lys Thr Ser Cys His Val Ser Trp Ala Pro
    12210           12215           12220                   1
Pro Glu Asn Asp Gly Gly Ser Gln Val Thr His Tyr Ile Val Glu Lys
2225            12230           12235                   12240
Arg Glu Ala Asp Arg Lys Thr Trp Ser Thr Val Thr Pro Glu Val Lys
            12245           12250           12255
Lys Thr Ser Phe His Val Thr Asn Leu Val Pro Gly Asn Glu Tyr Tyr
            12260           12265           12270
Phe Arg Val Thr Ala Val Asn Glu Tyr Gly Pro Gly Val Pro Thr Asp
        12275           12280           12285
Val Pro Lys Pro Val Leu Ala Ser Asp Pro Leu Ser Glu Pro Asp Pro
    12290           12295           12300                   1
Pro Arg Lys Leu Glu Ala Thr Glu Met Thr Lys Asn Ser Ala Thr Leu
2305            12310           12315                   12320
Ala Trp Leu Pro Pro Leu Arg Asp Gly Gly Ala Lys Ile Asp Gly Tyr
            12325           12330           12335
Ile Ile Ser Tyr Arg Glu Glu Glu Gln Pro Ala Asp Arg Trp Thr Glu
        12340           12345           12350
Tyr Ser Val Val Lys Asp Leu Ser Leu Val Val Thr Gly Leu Lys Glu
        12355           12360           12365
Gly Lys Lys Tyr Lys Phe Arg Val Ala Ala Arg Asn Ala Val Gly Val
    12370           12375           12380                   1
Ser Leu Pro Arg Glu Ala Glu Gly Val Tyr Glu Ala Lys Glu Gln Leu
2385            12390           12395                   12400
Leu Pro Pro Lys Ile Leu Met Pro Glu Gln Ile Thr Ile Lys Ala Gly
            12405           12410           12415
Lys Lys Leu Arg Ile Glu Ala His Val Tyr Gly Lys Pro His Pro Thr
        12420           12425           12430
Cys Lys Trp Lys Lys Gly Glu Asp Glu Val Val Thr Ser Ser His Leu
        12435           12440           12445
Ala Val His Lys Ala Asp Ser Ser Ser Ile Leu Ile Ile Lys Asp Val
    12450           12455           12460                   1
Thr Arg Lys Asp Ser Gly Tyr Tyr Ser Leu Thr Ala Glu Asn Ser Ser
2465            12470           12475                   12480
Gly Thr Asp Thr Gln Lys Ile Lys Val Val Val Met Asp Ala Pro Gly
            12485           12490           12495
Pro Pro Gln Pro Pro Phe Asp Ile Ser Asp Ile Asp Ala Asp Ala Cys
        12500           12505           12510
Ser Leu Ser Trp His Ile Pro Leu Glu Asp Gly Gly Ser Asn Ile Thr
        12515           12520           12525
Asn Tyr Ile Val Glu Lys Cys Asp Val Ser Arg Gly Asp Trp Val Thr
    12530           12535           12540                   1
Ala Leu Ala Ser Val Thr Lys Thr Ser Cys Arg Val Gly Lys Leu Ile
2545            12550           12555                   12560
Pro Gly Gln Glu Tyr Ile Phe Arg Val Arg Ala Glu Asn Arg Phe Gly
            12565           12570           12575
Ile Ser Glu Pro Leu Thr Ser Pro Lys Met Val Ala Gln Phe Pro Phe
        12580           12585           12590
Gly Val Pro Ser Glu Pro Lys Asn Ala Arg Val Thr Lys Val Asn Lys
        12595           12600           12605
Asp Cys Ile Phe Val Ala Trp Asp Arg Pro Asp Ser Asp Gly Gly Ser
    12610           12615           12620                   1
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Pro Ile Ile Gly Tyr Leu Ile Glu Arg Lys Glu Arg Asn Ser Leu Leu
2625   12630   12635   12640
Trp Val Lys Ala Asn Asp Thr Leu Val Arg Ser Thr Glu Tyr Pro Cys
            12645   12650   12655
Ala Gly Leu Val Glu Gly Leu Glu Tyr Ser Phe Arg Ile Tyr Ala Leu
            12660   12665   12670
Asn Lys Ala Gly Ser Ser Pro Pro Ser Lys Pro Thr Glu Tyr Val Thr
        12675   12680   12685
Ala Arg Met Pro Val Asp Pro Pro Gly Lys Pro Glu Val Ile Asp Val
        12690   12695   12700   1
Thr Lys Ser Thr Val Ser Leu Ile Trp Ala Arg Pro Lys His Asp Gly
2705   12710   12715   12720
Gly Ser Lys Ile Ile Gly Tyr Phe Val Glu Ala Cys Lys Leu Pro Gly
            12725   12730   12735
Asp Lys Trp Val Arg Cys Asn Thr Ala Pro His Gln Ile Pro Gln Glu
        12740   12745   12750
Glu Tyr Thr Ala Thr Gly Leu Glu Glu Lys Ala Gln Tyr Gln Phe Arg
        12755   12760   12765
Ala Ile Ala Arg Thr Ala Val Asn Ile Ser Pro Pro Ser Glu Pro Ser
        12770   12775   12780   1
Asp Pro Val Thr Ile Leu Ala Glu Asn Val Pro Pro Arg Ile Asp Leu
2785   12790   12795   12800
Ser Val Ala Met Lys Ser Leu Leu Thr Val Lys Ala Gly Thr Asn Val
            12805   12810   12815
Cys Leu Asp Ala Thr Val Phe Gly Lys Pro Met Pro Thr Val Ser Trp
        12820   12825   12830
Lys Lys Asp Gly Thr Leu Leu Lys Pro Ala Glu Gly Ile Lys Met Ala
        12835   12840   12845
Met Gln Arg Asn Leu Cys Thr Leu Glu Leu Phe Ser Val Asn Arg Lys
        12850   12855   12860   1
Asp Ser Gly Asp Tyr Thr Ile Thr Ala Glu Asn Ser Ser Gly Ser Lys
2865   12870   12875   12880
Ser Ala Thr Ile Lys Leu Lys Val Leu Asp Lys Pro Gly Pro Pro Ala
            12885   12890   12895
Ser Val Lys Ile Asn Lys Met Tyr Ser Asp Arg Ala Met Leu Ser Trp
        12900   12905   12910
Glu Pro Pro Leu Glu Asp Gly Gly Ser Glu Ile Thr Asn Tyr Ile Val
        12915   12920   12925
Asp Lys Arg Glu Thr Ser Arg Pro Asn Trp Ala Gln Val Ser Ala Thr
        12930   12935   12940   1
Val Pro Ile Thr Ser Cys Ser Val Glu Lys Leu Ile Glu Gly His Glu
2945   12950   12955   12960
Tyr Gln Phe Arg Ile Cys Ala Glu Asn Lys Tyr Gly Val Gly Asp Pro
            12965   12970   12975
Val Phe Thr Glu Pro Ala Ile Ala Lys Asn Pro Tyr Asp Pro Pro Gly
        12980   12985   12990
Arg Cys Asp Pro Pro Val Ile Ser Asn Ile Thr Lys Asp His Met Thr
        12995   13000   13005
Val Ser Trp Lys Pro Pro Ala Asp Asp Gly Gly Ser Pro Ile Thr Gly
        13010   13015   13020   1
Tyr Leu Leu Glu Lys Arg Glu Thr Gln Ala Val Asn Trp Thr Lys Val
3025   13030   13035   13040
Asn Arg Lys Pro Ile Ile Glu Arg Thr Leu Lys Ala Thr Gly Leu Gln
            13045   13050   13055
Glu Gly Thr Glu Tyr Glu Phe Arg Val Thr Ala Ile Asn Lys Ala Gly
        13060   13065   13070
Pro Gly Lys Pro Ser Asp Ala Ser Lys Ala Ala Tyr Ala Arg Asp Pro
        13075   13080   13085
Gln Tyr Pro Pro Ala Pro Pro Ala Phe Pro Lys Val Tyr Asp Thr Thr
        13090   13095   13100   1
Arg Ser Ser Val Ser Leu Ser Trp Gly Lys Pro Ala Tyr Asp Gly Gly
3105   13110   13115   13120

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Ser Pro Ile Ile Gly Tyr Leu Val Glu Val Lys Arg Ala Asp Ser Asp
          13125              13130              13135
Asn Trp Val Arg Cys Asn Leu Pro Gln Asn Leu Gln Lys Thr Arg Phe
          13140              13145              13150
Glu Val Thr Gly Leu Met Glu Asp Thr Gln Tyr Gln Phe Arg Val Tyr
          13155              13160              13165
Ala Val Asn Lys Ile Gly Tyr Ser Asp Pro Ser Asp Val Pro Asp Lys
     13170              13175              13180              1
His Tyr Pro Lys Asp Ile Leu Ile Pro Pro Glu Gly Glu His Asp Ala
3185              13190              13195              13200
Asp Leu Arg Lys Thr Leu Ile Leu Arg Ala Gly Val Thr Met Arg Leu
          13205              13210              13215
Tyr Val Pro Val Lys Gly Arg Pro Pro Pro Lys Ile Thr Trp Ser Lys
          13220              13225              13230
Pro Asn Val Asn Leu Arg Asp Arg Ile Gly Leu Asp Ile Lys Ser Thr
     13235              13240              13245
Asp Phe Asp Thr Phe Leu Arg Cys Glu Asn Val Asn Lys Tyr Asp Ala
     13250              13255              13260              1
Gly Lys Tyr Ile Leu Thr Leu Glu Asn Ser Cys Gly Lys Lys Glu Tyr
3265              13270              13275              13280
Thr Ile Val Val Lys Val Leu Asp Thr Pro Gly Pro Pro Ile Asn Val
          13285              13290              13295
Thr Val Lys Glu Ile Ser Lys Asp Ser Ala Tyr Val Thr Trp Glu Pro
          13300              13305              13310
Pro Ile Ile Asp Gly Gly Ser Pro Ile Ile Asn Tyr Val Val Gln Lys
     13315              13320              13325
Arg Asp Ala Glu Arg Lys Ser Trp Ser Thr Val Thr Thr Glu Cys Ser
     13330              13335              13340              1
Lys Thr Ser Phe Arg Val Pro Asn Leu Glu Glu Gly Lys Ser Tyr Phe
3345              13350              13355              13360
Phe Arg Val Phe Ala Glu Asn Glu Tyr Gly Ile Gly Asp Pro Gly Glu
          13365              13370              13375
Thr Arg Asp Ala Val Lys Ala Ser Gln Thr Pro Gly Pro Val Val Asp
          13380              13385              13390
Leu Lys Val Arg Ser Val Ser Lys Ser Ser Cys Ser Ile Gly Trp Lys
          13395              13400              13405
Lys Pro His Ser Asp Gly Gly Ser Arg Ile Ile Gly Tyr Val Val Asp
     13410              13415              13420              1
Phe Leu Thr Glu Glu Asn Lys Trp Gln Arg Val Met Lys Ser Leu Ser
3425              13430              13435              13440
Leu Gln Tyr Ser Ala Lys Asp Leu Thr Glu Gly Lys Glu Tyr Thr Phe
          13445              13450              13455
Arg Val Ser Ala Glu Asn Glu Asn Gly Glu Gly Thr Pro Ser Glu Ile
          13460              13465              13470
Thr Val Val Ala Arg Asp Asp Val Val Ala Pro Asp Leu Asp Leu Lys
     13475              13480              13485
Gly Leu Pro Asp Leu Cys Tyr Leu Ala Lys Glu Asn Ser Asn Phe Arg
     13490              13495              13500              1
Leu Lys Ile Pro Ile Lys Gly Lys Pro Ala Pro Ser Val Ser Trp Lys
3505              13510              13515              13520
Lys Gly Glu Asp Pro Leu Ala Thr Asp Thr Arg Val Ser Val Glu Ser
          13525              13530              13535
Ser Ala Val Asn Thr Thr Leu Ile Val Tyr Asp Cys Gln Lys Ser Asp
          13540              13545              13550
Ala Gly Lys Tyr Thr Ile Thr Leu Lys Asn Val Ala Gly Thr Lys Glu
     13555              13560              13565
Gly Thr Ile Ser Ile Lys Val Val Gly Lys Pro Gly Ile Pro Thr Gly
     13570              13575              13580              1
Pro Ile Lys Phe Asp Glu Val Thr Ala Glu Ala Met Thr Leu Lys Trp
3585              13590              13595              13600
Ala Pro Pro Lys Asp Asp Gly Gly Ser Glu Ile Thr Asn Tyr Ile Leu
          13605              13610              13615
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Glu Lys Arg Asp Ser Val Asn Asn Lys Trp Val Thr Cys Ala Ser Ala
        13620             13625                 13630
Val Gln Lys Thr Thr Phe Arg Val Thr Arg Leu His Glu Gly Met Glu
        13635             13640                 13645
Tyr Thr Phe Arg Val Ser Ala Glu Asn Lys Tyr Gly Val Gly Glu Gly
        13650             13655                 13660              1
Leu Lys Ser Glu Pro Ile Val Ala Arg His Pro Phe Asp Val Pro Asp
3665            13670             13675                 13680
Ala Pro Pro Pro Pro Asn Ile Val Asp Val Arg His Asp Ser Val Ser
        13685             13690                 13695
Leu Thr Trp Thr Asp Pro Lys Lys Thr Gly Gly Ser Pro Ile Thr Gly
        13700             13705                 13710
Tyr His Leu Glu Phe Lys Glu Arg Asn Ser Leu Leu Trp Lys Arg Ala
        13715             13720                 13725
Asn Lys Thr Pro Ile Arg Met Arg Asp Phe Lys Val Thr Gly Leu Thr
        13730             13735             13740              1
Glu Gly Leu Glu Tyr Glu Phe Arg Val Met Ala Ile Asn Leu Ala Gly
3745            13750             13755                 13760
Val Gly Lys Pro Ser Leu Pro Ser Glu Pro Val Val Ala Leu Asp Pro
            13765             13770                 13775
Ile Asp Pro Pro Gly Lys Pro Glu Val Ile Asn Ile Thr Arg Asn Ser
        13780             13785             13790
Val Thr Leu Ile Trp Thr Glu Pro Lys Tyr Asp Gly Gly His Lys Leu
        13795             13800             13805
Thr Gly Tyr Ile Val Glu Lys Arg Asp Leu Pro Ser Lys Ser Trp Met
        13810             13815             13820              1
Lys Ala Asn His Val Asn Val Pro Glu Cys Ala Phe Thr Val Thr Asp
3825            13830             13835                 13840
Leu Val Glu Gly Gly Lys Tyr Glu Phe Arg Ile Arg Ala Lys Asn Thr
            13845             13850                 13855
Ala Gly Ala Ile Ser Ala Pro Ser Glu Ser Thr Glu Thr Ile Ile Cys
        13860             13865                 13870
Lys Asp Glu Tyr Glu Ala Pro Thr Ile Val Leu Asp Pro Thr Ile Lys
        13875             13880             13885
Asp Gly Leu Thr Ile Lys Ala Gly Asp Thr Ile Val Leu Asn Ala Ile
        13890             13895             13900              1
Ser Ile Leu Gly Lys Pro Leu Pro Lys Ser Ser Trp Ser Lys Ala Gly
3905            13910             13915                 13920
Lys Asp Ile Arg Pro Ser Asp Ile Thr Gln Ile Thr Ser Thr Pro Thr
            13925             13930                 13935
Ser Ser Met Leu Thr Ile Lys Tyr Ala Thr Arg Lys Asp Ala Gly Glu
        13940             13945                 13950
Tyr Thr Ile Thr Ala Thr Asn Pro Phe Gly Thr Lys Val Glu His Val
        13955             13960             13965
Lys Val Thr Val Leu Asp Val Pro Gly Pro Pro Gly Pro Val Glu Ile
        13970             13975             13980              1
Ser Asn Val Ser Ala Glu Lys Ala Thr Leu Thr Trp Thr Pro Pro Leu
3985        .    13990             13995                 14000
Glu Asp Gly Gly Ser Pro Ile Lys Ser Tyr Ile Leu Glu Lys Arg Glu
            14005             14010                 14015
Thr Ser Arg Leu Leu Trp Thr Val Val Ser Glu Asp Ile Gln Ser Cys
        14020             14025             14030
Arg His Val Ala Thr Lys Leu Ile Gln Gly Asn Glu Tyr Ile Phe Arg
        14035             14040             14045
Val Ser Ala Val Asn His Tyr Gly Lys Gly Glu Pro Val Gln Ser Glu
    14050             14055             14060              1
Pro Val Lys Met Val Asp Arg Phe Gly Pro Pro Gly Pro Pro Glu Lys
4065            14070             14075                 14080
Pro Glu Val Ser Asn Val Thr Lys Asn Thr Ala Thr Val Ser Trp Lys
            14085             14090                 14095
Arg Pro Val Asp Asp Gly Gly Ser Glu Ile Thr Gly Tyr His Val Glu
        14100             14105                 14110
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Arg Arg Glu Lys Lys Ser Leu Arg Trp Val Arg Ala Ile Lys Thr Pro
    14115               14120                14125
Val Ser Asp Leu Arg Cys Lys Val Thr Gly Leu Gln Glu Gly Ser Thr
    14130               14135                14140                1
Tyr Glu Phe Arg Val Ser Ala Glu Asn Arg Ala Gly Ile Gly Pro Pro
4145                14150                14155                14160
Ser Glu Ala Ser Asp Ser Val Leu Met Lys Asp Ala Ala Tyr Pro Pro
            14165               14170                14175
Gly Pro Pro Ser Asn Pro His Val Thr Asp Thr Thr Lys Lys Ser Ala
        14180               14185                14190
Ser Leu Ala Trp Gly Lys Pro His Tyr Asp Gly Gly Leu Glu Ile Thr
    14195               14200                14205
Gly Tyr Val Val Glu His Gln Lys Val Gly Asp Glu Ala Trp Ile Lys
    14210               14215                14220                1
Asp Thr Thr Gly Thr Ala Leu Arg Ile Thr Gln Phe Val Val Pro Asp
4225                14230                14235                14240
Leu Gln Thr Lys Glu Lys Tyr Asn Phe Arg Ile Ser Ala Ile Asn Asp
            14245               14250                14255
Ala Gly Val Gly Glu Pro Ala Val Ile Pro Asp Val Glu Ile Val Glu
        14260               14265                14270
Arg Glu Met Ala Pro Asp Phe Glu Leu Asp Ala Glu Leu Arg Arg Thr
    14275               14280                14285
Leu Val Val Arg Ala Gly Leu Ser Ile Arg Ile Phe Val Pro Ile Lys
    14290               14295                14300                1
Gly Arg Pro Ala Pro Glu Val Thr Trp Thr Lys Asp Asn Ile Asn Leu
4305                14310                14315                14320
Lys Asn Arg Ala Asn Ile Glu Asn Thr Glu Ser Phe Thr Leu Leu Ile
            14325               14330                14335
Ile Pro Glu Cys Asn Arg Tyr Asp Thr Gly Lys Phe Val Met Thr Ile
        14340               14345                14350
Glu Asn Pro Ala Gly Lys Lys Ser Gly Phe Val Asn Val Arg Val Leu
    14355               14360                14365
Asp Thr Pro Gly Pro Val Leu Asn Leu Arg Pro Thr Asp Ile Thr Lys
    14370               14375                14380                1
Asp Ser Val Thr Leu His Trp Asp Leu Pro Leu Ile Asp Gly Gly Ser
4385                14390                14395                14400
Arg Ile Thr Asn Tyr Ile Val Glu Lys Arg Glu Ala Thr Arg Lys Ser
            14405               14410                14415
Tyr Ser Thr Ala Thr Thr Lys Cys His Lys Cys Thr Tyr Lys Val Thr
        14420               14425                14430
Gly Leu Ser Glu Gly Cys Glu Tyr Phe Phe Arg Val Met Ala Glu Asn
    14435               14440                14445
Glu Tyr Gly Ile Gly Glu Pro Thr Glu Thr Glu Pro Val Lys Ala
    14450               14455                14460                1
Ser Glu Ala Pro Ser Pro Pro Asp Ser Leu Asn Ile Met Asp Ile Thr
4465                14470                14475                14480
Lys Ser Thr Val Ser Leu Ala Trp Pro Lys Pro Lys His Asp Gly Gly
            14485               14490                14495
Ser Lys Ile Thr Gly Tyr Val Ile Glu Ala Gln Arg Lys Gly Ser Asp
        14500               14505                14510
Gln Trp Thr His Ile Thr Thr Val Lys Gly Leu Glu Cys Val Val Arg
    14515               14520                14525
Asn Leu Thr Glu Gly Glu Glu Tyr Thr Phe Gln Val Met Ala Val Asn
    14530               14535                14540                1
Ser Ala Gly Arg Ser Ala Pro Arg Glu Ser Arg Pro Val Ile Val Lys
4545                14550                14555                14560
Glu Gln Thr Met Leu Pro Glu Leu Asp Leu Arg Gly Ile Tyr Gln Lys
            14565               14570                14575
Leu Val Ile Ala Lys Ala Gly Asp Asn Ile Lys Val Glu Ile Pro Val
        14580               14585                14590
Leu Gly Arg Pro Lys Pro Thr Val Thr Trp Lys Lys Gly Asp Gln Ile
    14595               14600                14605
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Leu Lys Gln Thr Gln Arg Val Asn Phe Glu Thr Thr Ala Thr Ser Thr
    14610                 14615                 14620                 1
Ile Leu Asn Ile Asn Glu Cys Val Arg Ser Asp Ser Gly Pro Tyr Pro
4625                 14630                 14635                 14640
Leu Thr Ala Arg Asn Ile Val Gly Glu Val Gly Asp Val Ile Thr Ile·
                14645                 14650                 14655
Gln Val His Asp Ile Pro Gly Pro Pro Thr Gly Pro Ile Lys Phe Asp
            14660                 14665                 14670
Glu Val Ser Ser Asp Phe Val Thr Phe Ser Trp Asp Pro Pro Glu Asn
    14675                 14680                 14685
Asp Gly Gly Val Pro Ile Ser Asn Tyr Val Val Glu Met Arg Gln Thr
    14690                 14695                 14700                 1
Asp Ser Thr Thr Trp Val Glu Leu Ala Thr Thr Val Ile Arg Thr Thr
4705                 14710                 14715                 14720
Tyr Lys Ala Thr Arg Leu Thr Thr Gly Leu Glu Tyr Gln Phe Arg Val
                14725                 14730                 14735
Lys Ala Gln Asn Arg Tyr Gly Val Gly Pro Gly Ile Thr Ser Ala Trp
            14740                 14745                 14750
Ile Val Ala Asn Tyr Pro Phe Lys Val Pro Gly Pro Pro Gly Thr Pro
            14755                 14760                 14765
Gln Val Thr Ala Val Thr Lys Asp Ser Met Thr Ile Ser Trp His Glu
    14770                 14775                 14780                 1
Pro Leu Ser Asp Gly Gly Ser Pro Ile Leu Gly Tyr His Val Glu Arg
4785                 14790                 14795                 14800
Lys Glu Arg Asn Gly Ile Leu Trp Gln Thr Val Ser Lys Ala Leu Val
            14805                 14810                 14815
Pro Gly Asn Ile Phe Lys Ser Ser Gly Leu Thr Asp Gly Ile Ala Tyr
            14820                 14825                 14830
Glu Phe Arg Val Ile Ala Glu Asn Met Ala Gly Lys Ser Lys Pro Ser
    14835                 14840                 14845 ·
Lys Pro Ser Glu Pro Met Leu Ala Leu Asp Pro Ile Asp Pro Pro Gly
    14850                 14855                 14860                 1
Lys Pro Val Pro Leu Asn Ile Thr Arg His Thr Val Thr Leu Lys Trp
4865                 14870                 14875                 14880
Ala Lys Pro Glu Tyr Thr Gly Gly Phe Lys Ile Thr Ser Tyr Ile Val
            14885                 14890                 14895
Glu Lys Arg Asp Leu Pro Asn Gly Arg Trp Leu Lys Ala Asn Phe Ser
    14900                 14905                 14910
Asn Ile Leu Glu Asn Glu Phe Thr Val Ser Gly Leu Thr Glu Asp Ala
    14915                 14920                 14925
Ala Tyr Glu Phe Arg Val Ile Ala Lys Asn Ala Ala Gly Ala Ile Ser
    14930                 14935                 14940                 1
Pro Pro Ser Glu Pro Ser Asp Ala Ile Thr Cys Arg Asp Asp Val Glu
4945                 14950          ,      14955                 14960
Ala Pro Lys Ile Lys Val Asp Val Lys Phe Lys Asp Thr Val Ile Leu
            14965                 14970                 14975
Lys Ala Gly Glu Ala Phe Arg Leu Glu Ala Asp Val Ser Gly Arg Pro
    14980                 14985                 14990
Pro Pro Thr Met Glu Trp Ser Lys Asp Gly Lys Glu Leu Glu Gly Thr
    14995                 15000                 15005
Ala Lys Leu Glu Ile Lys Ile Ala Asp Phe Ser Thr Asn Leu Val Asn
    15010                 15015                 15020                 1
Lys Asp Ser Thr Arg Arg Asp Ser Gly Ala Tyr Thr Leu Thr Ala Thr
5025                 15030                 15035                 15040
Asn Pro Gly Gly Phe Ala Lys His Ile Phe Asn Val Lys Val Leu Asp
            15045                 15050                 15055
Arg Pro Gly Pro Pro Glu Gly Pro Leu Ala Val Thr Glu Val Thr Ser
        15060                 15065                 15070
Glu Lys Cys Val Leu Ser Trp Phe Pro Pro Leu Asp Asp Gly Gly Ala
    15075                 15080                 15085
Lys Ile Asp His Tyr Ile Val Gln Lys Arg Glu Thr Ser Arg Leu Ala
    15090                 15095                 15100                 1
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Trp Thr Asn Val Ala Ser Glu Val Gln Val Thr Lys Leu Lys Val Thr
5105            15110            15115            15120
Lys Leu Leu Lys Gly Asn Glu Tyr Ile Phe Arg Val Met Ala Val Asn
        15125            15130            15135
Lys Tyr Gly Val Gly Glu Pro Leu Glu Ser Glu Pro Val Leu Ala Val
        15140            15145            15150
Asn Pro Tyr Gly Pro Pro Asp Pro Pro Lys Asn Pro Glu Val Thr Thr
        15155            15160            15165
Ile Thr Lys Asp Ser Met Val Val Cys Trp Gly His Pro Asp Ser Asp
    15170            15175            15180            1
Gly Gly Ser Glu Ile Ile Asn Tyr Ile Val Glu Arg Arg Asp Lys Ala
5185            15190            15195            15200
Gly Gln Arg Trp Ile Lys Cys Asn Lys Lys Thr Leu Thr Asp Leu Arg
        15205            15210            15215
Tyr Lys Val Ser Gly Leu Thr Glu Gly His Glu Tyr Glu Phe Arg Ile
        15220            15225            15230
Met Ala Glu Asn Ala Ala Gly Ile Ser Ala Pro Ser Pro Thr Ser Pro
        15235            15240            15245
Phe Tyr Lys Ala Cys Asp Thr Val Phe Lys Pro Gly Pro Pro Gly Asn
    15250            15255            15260            1
Pro Arg Val Leu Asp Thr Ser Arg Ser Ser Ile Ser Ile Ala Trp Asn
5265            15270            15275            15280
Lys Pro Ile Tyr Asp Gly Gly Ser Glu Ile Thr Gly Tyr Met Val Glu
        15285            15290            15295
Ile Ala Leu Pro Glu Glu Asp Glu Trp Gln Ile Val Thr Pro Pro Ala
        15300            15305            15310
Gly Leu Lys Ala Thr Ser Tyr Thr Ile Thr Gly Leu Thr Glu Asn Gln
        15315            15320            15325
Glu Tyr Lys Ile Arg Ile Tyr Ala Met Asn Ser Glu Gly Leu Gly Glu
    15330            15335            15340            1
Pro Ala Leu Val Pro Gly Thr Pro Lys Ala Glu Asp Arg Met Leu Pro
5345            15350            15355            15360
Pro Glu Ile Glu Leu Asp Ala Asp Leu Arg Lys Val Val Thr Ile Arg
        15365            15370            15375
Ala Cys Cys Thr Leu Arg Leu Phe Val Pro Ile Lys Gly Arg Pro Asp
        15380            15385            15390
Pro Glu Val Lys Trp Ala Arg Asp His Gly Glu Ser Leu Asp Lys Ala
    15395            15400            15405
Ser Ile Glu Ser Ala Ser Ser Tyr Thr Leu Leu Ile Val Gly Asn Val
    15410            15415            15420            1
Asn Arg Phe Asp Ser Gly Lys Tyr Ile Leu Thr Val Glu Asn Ser Ser
5425            15430            15435            15440
Gly Ser Lys Ser Ala Phe Val Asn Val Arg Val Leu Asp Thr Pro Gly
        15445            15450            15455
Pro Pro Gln Asp Leu Lys Val Lys Glu Val Thr Lys Thr Ser Val Thr
        15460            15465            15470
Leu Thr Trp Asp Pro Pro Leu Leu Asp Gly Gly Ser Lys Ile Lys Asn
    15475            15480            15485
Tyr Ile Val Glu Lys Arg Glu Ser Thr Arg Lys Ala Tyr Ser Thr Val
    15490            15495            15500            1
Ala Thr Asn Cys His Lys Thr Ser Trp Lys Val Asp Gln Leu Gln Glu
5505            15510            15515            15520
Gly Cys Ser Tyr Tyr Phe Arg Val Leu Ala Glu Asn Glu Tyr Gly Ile
        15525            15530            15535
Gly Leu Pro Ala Glu Thr Ala Glu Ser Val Lys Ala Ser Glu Arg Pro
        15540            15545            15550
Leu Pro Pro Gly Lys Ile Thr Leu Met Asp Val Thr Arg Asn Ser Val
    15555            15560            15565
Ser Leu Ser Trp Glu Lys Pro Glu His Asp Gly Gly Ser Arg Ile Leu
    15570            15575            15580            1
Gly Tyr Ile Val Glu Met Gln Thr Lys Gly Ser Asp Lys Trp Ala Thr
5585            15590            15595            15600
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Cys Ala Thr Val Lys Val Thr Glu Ala Thr Ile Thr Gly Leu Ile Gln
      15605   15610   15615
Gly Glu Glu Tyr Ser Phe Arg Val Ser Ala Gln Asn Glu Lys Gly Ile
      15620   15625   15630
Ser Asp Pro Arg Gln Leu Ser Val Pro Val Ile Ala Lys Asp Leu Val
    15635   15640   15645
Ile Pro Pro Ala Phe Lys Leu Leu Phe Asn Thr Phe Thr Val Leu Ala
   15650   15655   15660   1
Gly Glu Asp Leu Lys Val Asp Val Pro Phe Ile Gly Arg Pro Thr Pro
5665   15670   15675   15680
Ala Val Thr Trp His Lys Asp Asn Val Pro Leu Lys Gln Thr Thr Arg
      15685   15690   15695
Val Asn Ala Glu Ser Thr Glu Asn Asn Ser Leu Leu Thr Ile Lys Asp
     15700   15705   15710
Ala Cys Arg Glu Asp Val Gly His Tyr Val Val Lys Leu Thr Asn Ser
     15715   15720   15725
Ala Gly Glu Ala Ile Glu Thr Leu Asn Val Ile Val Leu Asp Lys Pro
    15730   15735   15740   1
Gly Pro Pro Thr Gly Pro Val Lys Met Asp Glu Val Thr Ala Asp Ser
5745   15750   15755   15760
Ile Thr Leu Ser Trp Gly Pro Pro Lys Tyr Asp Gly Gly Ser Ser Ile
      15765   15770   15775
Asn Asn Tyr Ile Val Glu Lys Arg Asp Thr Ser Thr Thr Thr Trp Gln
     15780   15785   15790
Ile Val Ser Ala Thr Val Ala Arg Thr Thr Ile Lys Ala Cys Arg Leu
    15795   15800   15805
Lys Thr Gly Cys Glu Tyr Gln Phe Arg Ile Ala Ala Glu Asn Arg Tyr
   15810   15815   15820   1
Gly Lys Ser Thr Tyr Leu Asn Ser Glu Pro Thr Val Ala Gln Tyr Pro
5825   15830   15835   15840
Phe Lys Val Pro Gly Pro Pro Gly Thr Pro Val Val Thr Leu Ser Ser
      15845   15850   15855
Arg Asp Ser Met Glu Val Gln Trp Asn Glu Pro Ile Ser Asp Gly Gly
     15860   15865   15870
Ser Arg Val Ile Gly Tyr His Leu Glu Arg Lys Glu Arg Asn Ser Ile
    15875   15880   15885
Leu Trp Val Lys Leu Asn Lys Thr Pro Ile Pro Gln Thr Lys Phe Lys
   15890   15895   15900   1
Thr Thr Gly Leu Glu Glu Gly Val Glu Tyr Glu Phe Arg Val Ser Ala
5905   15910   15915   15920
Glu Asn Ile Val Gly Ile Gly Lys Pro Ser Lys Val Ser Glu Cys Tyr
      15925   15930   15935
Val Ala Arg Asp Pro Cys Asp Pro Pro Gly Arg Pro Glu Ala Ile Ile
     15940   15945   15950
Val Thr Arg Asn Ser Val Thr Leu Gln Trp Lys Lys Pro Thr Tyr Asp
     15955   15960   15965
Gly Gly Ser Lys Ile Thr Gly Tyr Ile Val Glu Lys Lys Glu Leu Pro
    15970   15975   15980   1
Glu Gly Arg Trp Met Lys Ala Ser Phe Thr Asn Ile Ile Asp Thr His
5985   15990   15995   16000
Phe Glu Val Thr Gly Leu Val Glu Asp His Arg Tyr Glu Phe Arg Val
      16005   16010   16015
Ile Ala Arg Asn Ala Ala Gly Val Phe Ser Glu Pro Ser Glu Ser Thr
      16020   16025   16030
Gly Ala Ile Thr Ala Arg Asp Glu Val Asp Pro Pro Arg Ile Ser Met
    16035   16040   16045
Asp Pro Lys Tyr Lys Asp Thr Ile Val Val His Ala Gly Glu Ser Phe
   16050   16055   16060   1
Lys Val Asp Ala Asp Ile Tyr Gly Lys Pro Ile Pro Thr Ile Gln Trp
6065   16070   16075   16080
Ile Lys Gly Asp Gln Glu Leu Ser Asn Thr Ala Arg Leu Glu Ile Lys
     16085   16090   16095

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Ser Thr Asp Phe Ala Thr Ser Leu Ser Val Lys Asp Ala Val Arg Val
        16100              16105              16110
Asp Ser Gly Asn Tyr Ile Leu Lys Ala Lys Asn Val Ala Gly Glu Arg
        16115              16120              16125
Ser Val Thr Val Asn Val Lys Val Leu Asp Arg Pro Gly Pro Pro Glu
      16130              16135              16140            1
Gly Pro Val Val Ile Ser Gly Val Thr Ala Glu Lys Cys Thr Leu Ala
6145              16150              16155              16160
Trp Lys Pro Pro Leu Gln Asp Gly Gly Ser Asp Ile Ile Asn Tyr Ile
           16165              16170              16175
Val Glu Arg Arg Glu Thr Ser Arg Leu Val Trp Thr Val Val Asp Ala
        16180              16185              16190
Asn Val Gln Thr Leu Ser Cys Lys Val Thr Lys Leu Leu Glu Gly Asn
      16195              16200              16205
Glu Tyr Thr Phe Arg Ile Met Ala Val Asn Lys Tyr Gly Val Gly Glu
    16210              16215              16220            1
Pro Leu Glu Ser Glu Pro Val Val Ala Lys Asn Pro Phe Val Val Pro
6225              16230              16235              16240
Asp Ala Pro Lys Ala Pro Glu Val Thr Thr Val Thr Lys Asp Ser Met
           16245              16250              16255
Ile Val Val Trp Glu Arg Pro Ala Ser Asp Gly Gly Ser Glu Ile Leu
        16260              16265              16270
Gly Tyr Val Leu Glu Lys Arg Asp Lys Glu Gly Ile Arg Trp Thr Arg
      16275              16280              16285
Cys His Lys Arg Leu Ile Gly Glu Leu Arg Leu Arg Val Thr Gly Leu
    16290              16295              16300            1
Ile Glu Asn His Asp Tyr Glu Phe Arg Val Ser Ala Glu Asn Ala Ala
6305              16310              16315              16320
Gly Leu Ser Glu Pro Ser Pro Pro Ser Ala Tyr Gln Lys Ala Cys Asp
           16325              16330              16335
Pro Ile Tyr Lys Pro Gly Pro Pro Asn Asn Pro Lys Val Ile Asp Ile
        16340              16345              16350
Thr Arg Ser Ser Val Phe Leu Ser Trp Ser Lys Pro Ile Tyr Asp Gly
      16355              16360              16365
Gly Cys Glu Ile Gln Gly Tyr Ile Val Glu Lys Cys Asp Val Asn Val
    16370              16375              16380            1
Gly Glu Trp Thr Met Cys Thr Pro Pro Thr Gly Ile Asn Lys Thr Asn
6385              16390              16395              16400
Ile Glu Val Glu Lys Leu Leu Glu Lys His Glu Tyr Asn Phe Arg Ile
           16405              16410              16415
Cys Ala Ile Asn Lys Ala Gly Val Gly Glu His Ala Asp Val Pro Gly
        16420              16425              16430
Pro Ile Ile Val Glu Glu Lys Leu Glu Ala Pro Asp Ile Asp Leu Asp
      16435              16440              16445
Leu Glu Leu Arg Lys Ile Ile Asn Ile Arg Ala Gly Gly Ser Leu Arg
    16450              16455              16460            1
Leu Phe Val Pro Ile Lys Gly Arg Pro Thr Pro Glu Val Lys Trp Gly
6465              16470              16475              16480
Lys Val Asp Gly Glu Ile Arg Asp Ala Ala Ile Ile Asp Val Thr Ser
           16485              16490              16495
Ser Phe Thr Ser Leu Val Leu Asp Asn Val Asn Arg Tyr Asp Ser Gly
        16500              16505              16510
Lys Tyr Thr Leu Thr Leu Glu Asn Ser Ser Gly Thr Lys Ser Ala Phe
      16515              16520              16525
Val Thr Val Arg Val Leu Asp Thr Pro Ser Pro Pro Val Asn Leu Lys
    16530              16535              16540            1
Val Thr Glu Ile Thr Lys Asp Ser Val Ser Ile Thr Trp Glu Pro Pro
6545              16550              16555              16560
Leu Leu Asp Gly Gly Ser Lys Ile Lys Asn Tyr Ile Val Glu Lys Arg
           16565              16570              16575
Glu Ala Thr Arg Lys Ser Tyr Ala Ala Val Val Thr Asn Cys His Lys
      16580              16585              16590
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Asn Ser Trp Lys Ile Asp Gln Leu Gln Glu Gly Cys Ser Tyr Tyr Phe
      16595                16600                16605
Arg Val Thr Ala Glu Asn Glu Tyr Gly Ile Gly Leu Pro Ala Gln Thr
      16610                16615                16620                1
Ala Asp Pro Ile Lys Val Ala Glu Val Pro Gln Pro Pro Gly Lys Ile
6625                16630                16635                16640
Thr Val Asp Asp Val Thr Arg Asn Ser Val Ser Leu Ser Trp Thr Lys
           16645                16650                16655
Pro Glu His Asp Gly Gly Ser Lys Ile Ile Gln Tyr Ile Val Glu Met
      16660                16665                16670
Gln Ala Lys His Ser Glu Lys Trp Ser Glu Cys Ala Arg Val Lys Ser
      16675                16680                16685
Leu Gln Ala Val Ile Thr Asn Leu Thr Gln Gly Glu Glu Tyr Leu Phe
      16690                16695                16700                1
Arg Val Val Ala Val Asn Glu Lys Gly Arg Ser Asp Pro Arg Ser Leu
6705                16710                16715                16720
Ala Val Pro Ile Val Ala Lys Asp Leu Val Ile Glu Pro Asp Val Lys
           16725                16730                16735
Pro Ala Phe Ser Ser Tyr Ser Val Gln Val Gly Gln Asp Leu Lys Ile
      16740                16745                16750
Glu Val Pro Ile Ser Gly Arg Pro Lys Pro Thr Ile Thr Trp Thr Lys
      16755                16760                16765
Asp Gly Leu Pro Leu Lys Gln Thr Thr Arg Ile Asn Val Thr Asp Ser
      16770                16775                16780                1
Leu Asp Leu Thr Thr Leu Ser Ile Lys Glu Thr His Lys Asp Asp Gly
6785                16790                16795                16800
Gly Gln Tyr Gly Ile Thr Val Ala Asn Val Val Gly Gln Lys Thr Ala
           16805                16810                16815
Ser Ile Glu Ile Val Thr Leu Asp Lys Pro Asp Pro Pro Lys Gly Pro
      16820                16825                16830
Val Lys Phe Asp Asp Val Ser Ala Glu Ser Ile Thr Leu Ser Trp Asn
      16835                16840                16845
Pro Pro Leu Tyr Thr Gly Gly Cys Gln Ile Thr Asn Tyr Ile Val Gln
      16850                16855                16860                1
Lys Arg Asp Thr Thr Thr Thr Val Trp Asp Val Val Ser Ala Thr Val
6865                16870                16875                16880
Ala Arg Thr Thr Leu Lys Val Thr Lys Leu Lys Thr Gly Thr Glu Tyr
           16885                16890                16895
Gln Phe Arg Ile Phe Ala Glu Asn Arg Tyr Gly Gln Ser Phe Ala Leu
      16900                16905                16910
Glu Ser Asp Pro Ile Val Ala Gln Tyr Pro Tyr Lys Glu Pro Gly Pro
      16915                16920                16925
Pro Gly Thr Pro Phe Ala Thr Ala Ile Ser Lys Asp Ser Met Val Ile
      16930                16935                16940                1
Gln Trp His Glu Pro Val Asn Asn Gly Gly Ser Pro Val Ile Gly Tyr
6945                16950                16955                16960
His Leu Glu Arg Lys Glu Arg Asn Ser Ile Leu Trp Thr Lys Val Asn
           16965                16970                16975
Lys Thr Ile Ile His Asp Thr Gln Phe Lys Ala Gln Asn Leu Glu Glu
      16980                16985                16990
Gly Ile Glu Tyr Glu Phe Arg Val Tyr Ala Glu Asn Ile Val Gly Val
      16995                17000                17005
Gly Lys Ala Ser Lys Asn Ser Glu Cys Tyr Val Ala Arg Asp Pro Cys
  17010                17015                17020                1
Asp Pro Pro Gly Thr Pro Glu Pro Ile Met Val Lys Arg Asn Glu Ile
7025                17030                17035                17040
Thr Leu Gln Trp Thr Lys Pro Val Tyr Asp Gly Gly Ser Met Ile Thr
           17045                17050                17055
Gly Tyr Ile Val Glu Lys Arg Asp Leu Pro Asp Gly Arg Trp Met Lys
      17060                17065                17070
Ala Ser Phe Thr Asn Val Ile Glu Thr Gln Phe Thr Val Ser Gly Leu
      17075                17080                17085
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Thr Glu Asp Gln Arg Tyr Glu Phe Arg Val Ile Ala Lys Asn Ala Ala
    17090                17095               17100                    1
Gly Ala Ile Ser Lys Pro Ser Asp Ser Thr Gly Pro Ile Thr Ala Lys
7105              17110              17115                    17120
Asp Glu Val Glu Leu Pro Arg Ile Ser Met Asp Pro Lys Phe Arg Asp
                17125               17130               17135
Thr Ile Val Val Asn Ala Gly Glu Thr Phe Arg Leu Glu Ala Asp Val
        17140               17145               17150
His Gly Lys Pro Leu Pro Thr Ile Glu Trp Leu Arg Gly Asp Lys Glu
        17155               17160               17165
Ile Glu Ser Ala Arg Cys Glu Ile Lys Asn Thr Asp Phe Lys Ala
    17170               17175               17180                    1
Leu Leu Ile Val Lys Asp Ala Ile Arg Ile Asp Gly Gly Gln Tyr Ile
7185              17190              17195                    17200
Leu Arg Ala Ser Asn Val Ala Gly Ser Lys Ser Phe Pro Val Asn Val
                17205               17210               17215
Lys Val Leu Asp Arg Pro Gly Pro Pro Glu Gly Pro Val Gln Val Thr
        17220               17225               17230
Gly Val Thr Ser Glu Lys Cys Ser Leu Thr Trp Ser Pro Pro Leu Gln
        17235               17240               17245
Asp Gly Gly Ser Asp Ile Ser His Tyr Val Val Glu Lys Arg Glu Thr
        17250               17255               17260                1
Ser Arg Leu Ala Trp Thr Val Val Ala Ser Glu Val Val Thr Asn Ser
7265              17270              17275                    17280
Leu Lys Val Thr Lys Leu Leu Glu Gly Asn Glu Tyr Val Phe Arg Ile
                17285               17290               17295
Met Ala Val Asn Lys Tyr Gly Val Gly Glu Pro Leu Glu Ser Ala Pro
        17300               17305               17310
Val Leu Met Lys Asn Pro Phe Val Leu Pro Gly Pro Pro Lys Ser Leu
        17315               17320               17325
Glu Val Thr Asn Ile Ala Lys Asp Ser Met Thr Val Cys Trp Asn Arg
    17330               17335               17340                    1
Pro Asp Ser Asp Gly Gly Ser Glu Ile Ile Gly Tyr Ile Val Glu Lys
7345              17350              17355                    17360
Arg Asp Arg Ser Gly Ile Arg Trp Ile Lys Cys Asn Lys Arg Arg Ile
                17365               17370               17375
Thr Asp Leu Arg Leu Arg Val Thr Gly Leu Thr Glu Asp His Glu Tyr
        17380               17385               17390
Glu Phe Arg Val Ser Ala Glu Asn Ala Ala Gly Val Gly Glu Pro Ser
        17395               17400               17405
Pro Ala Thr Val Tyr Tyr Lys Ala Cys Asp Pro Val Phe Lys Pro Gly
    17410               17415               17420                    1
Pro Pro Thr Asn Ala His Ile Val Asp Thr Thr Lys Asn Ser Ile Thr
7425              17430              17435                    17440
Leu Ala Trp Gly Lys Pro Ile Tyr Asp Gly Gly Ser Glu Ile Leu Gly
                17445               17450               17455
Tyr Val Val Glu Ile Cys Lys Ala Asp Glu Glu Glu Trp Gln Ile Val
        17460               17465               17470
Thr Pro Gln Thr Gly Leu Arg Val Thr Arg Phe Glu Ile Ser Lys Leu
        17475               17480               17485
Thr Glu His Gln Glu Tyr Lys Ile Arg Val Cys Ala Leu Asn Lys Val
        17490               17495               17500                1
Gly Leu Gly Glu Ala Thr Ser Val Pro Gly Thr Val Lys Pro Glu Asp
7505              17510              17515                    17520
Lys Leu Glu Ala Pro Glu Leu Asp Leu Asp Ser Glu Leu Arg Lys Gly
                17525               17530               17535
Ile Val Val Arg Ala Gly Gly Ser Ala Arg Ile His Ile Pro Phe Lys
        17540               17545               17550
Gly Arg Pro Met Pro Glu Ile Thr Trp Ser Arg Glu Glu Gly Glu Phe
        17555               17560               17565
Thr Asp Lys Val Gln Ile Glu Lys Gly Val Asn Tyr Thr Gln Leu Ser
    17570               17575               17580                    1
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Ile Asp Asn Cys Asp Arg Asn Asp Ala Gly Lys Tyr Ile Leu Lys Leu
7585              17590              17595                  17600
Glu Asn Ser Ser Gly Ser Lys Ser Ala Phe Val Thr Val Lys Val Leu
            17605              17610              17615
Asp Thr Pro Gly Pro Pro Gln Asn Leu Ala Val Lys Glu Val Arg Lys
        17620              17625              17630
Asp Ser Ala Phe Leu Val Trp Glu Pro Pro Ile Ile Asp Gly Gly Ala
        17635              17640              17645
Lys Val Lys Asn Tyr Val Ile Asp Lys Arg Glu Ser Thr Arg Lys Ala
    17650              17655              17660                  1
Tyr Ala Asn Val Ser Ser Lys Cys Ser Lys Thr Ser Phe Lys Val Glu
7665              17670              17675                  17680
Asn Leu Thr Glu Gly Ala Ile Tyr Tyr Phe Arg Val Met Ala Glu Asn
            17685              17690              17695
Glu Phe Gly Val Gly Val Pro Val Glu Thr Val Asp Ala Val Lys Ala
        17700              17705              17710
Ala Glu Pro Pro Ser Pro Pro Gly Lys Val Thr Leu Thr Asp Val Ser
    17715              17720              17725
Gln Thr Ser Ala Ser Leu Met Trp Glu Lys Pro Glu His Asp Gly Gly
    17730              17735              17740                  1
Ser Arg Val Leu Gly Tyr Val Val Glu Met Gln Pro Lys Gly Thr Glu
7745              17750              17755                  17760
Lys Trp Ser Ile Val Ala Glu Ser Lys Val Cys Asn Ala Val Val Thr
            17765              17770              17775
Gly Leu Ser Ser Gly Gln Glu Tyr Gln Phe Arg Val Lys Ala Tyr Asn
        17780              17785              17790
Glu Lys Gly Lys Ser Asp Pro Arg Val Leu Gly Val Pro Val Ile Ala
        17795              17800              17805
Lys Asp Leu Thr Ile Gln Pro Ser Leu Lys Leu Pro Phe Asn Thr Tyr
    17810              17815              17820                  1
Ser Ile Gln Ala Gly Glu Asp Leu Lys Ile Glu Ile Pro Val Ile Gly
7825              17830              17835                  17840
Arg Pro Arg Pro Asn Ile Ser Trp Val Lys Asp Gly Glu Pro Leu Lys
            17845              17850              17855
Gln Thr Thr Arg Val Asn Val Glu Glu Thr Ala Thr Ser Thr Val Leu
        17860              17865              17870
His Ile Lys Glu Gly Asn Lys Asp Asp Phe Gly Lys Tyr Thr Val Thr
    17875              17880              17885
Ala Thr Asn Ser Ala Gly Thr Ala Thr Glu Asn Leu Ser Val Ile Val
    17890              17895              17900                  1
Leu Glu Lys Pro Gly Pro Pro Val Gly Pro Val Arg Phe Asp Glu Val
7905              17910              17915                  17920
Ser Ala Asp Phe Val Val Ile Ser Trp Glu Pro Pro Ala Tyr Thr Gly
            17925              17930              17935
Gly Cys Gln Ile Ser Asn Tyr Ile Val Glu Lys Arg Asp Thr Thr Thr
        17940              17945              17950
Thr Thr Trp His Met Val Ser Ala Thr Val Ala Arg Thr Thr Ile Lys
    17955              17960              17965
Ile Thr Lys Leu Lys Thr Gly Thr Glu Tyr Gln Phe Arg Ile Phe Ala
    17970              17975              17980                  1
Glu Asn Arg Tyr Gly Lys Ser Ala Pro Leu Asp Ser Lys Ala Val Ile
7985              17990              17995                  18000
Val Gln Tyr Pro Phe Lys Glu Pro Gly Pro Pro Gly Thr Pro Phe Val
            18005              18010              18015
Thr Ser Ile Ser Lys Asp Gln Met Leu Val Gln Trp His Glu Pro Val
        18020              18025              18030
Asn Asp Gly Gly Thr Lys Ile Ile Gly Tyr His Leu Glu Gln Lys Glu
        18035              18040              18045
Lys Asn Ser Ile Leu Trp Val Lys Leu Asn Lys Thr Pro Ile Gln Asp
    18050              18055               18060                 1
Thr Lys Phe Lys Thr Thr Gly Leu Asp Glu Gly Leu Glu Tyr Glu Phe
8065              18070              18075                  18080
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Lys Val Ser Ala Glu Asn Ile Val Gly Ile Gly Lys Pro Ser Lys Val
            18085   18090   18095
Ser Glu Cys Phe Val Ala Arg Asp Pro Cys Asp Pro Pro Gly Arg Pro
            18100   18105   18110
Glu Ala Ile Val Ile Thr Arg Asn Asn Val Thr Leu Lys Trp Lys Lys
            18115   .   18120   18125
Pro Ala Tyr Asp Gly Gly Ser Lys Ile Thr Gly Tyr Ile Val Glu Lys
            18130   18135   18140   1
Lys Asp Leu Pro Asp Gly Arg Trp Met Lys Ala Ser Phe Thr Asn Val
8145   18150   18155   .   18160
Leu Glu Thr Glu Phe Thr Val Ser Gly Leu Val Glu Asp Gln Arg Tyr
            18165   18170   18175
Glu Phe Arg Val Ile Ala Arg Asn Ala Ala Gly Asn Phe Ser Glu Pro
            18180   18185   18190
Ser Asp Ser Ser Gly Ala Ile Thr Ala Arg Asp Glu Ile Asp Ala Pro
            18195   18200   18205
Asn Ala Ser Leu Asp Pro Lys Tyr Lys Asp Val Ile Val Val His Ala
            18210   18215   18220   1
Gly Glu Thr Phe Val Leu Glu Ala Asp Ile Arg Gly Lys Pro Ile Pro
8225   18230   18235   18240
Asp Val Val Trp Ser Lys Asp Gly Lys Glu Leu Glu Glu Thr Ala Ala
            .18245   18250   18255
Arg Met Glu Ile Lys Ser Thr Ile Gln Lys Thr Thr Leu Val Val Lys
            18260   18265   18270
Asp Cys Ile Arg Thr Asp Gly Gly Gln Tyr Ile Leu Lys Leu Ser Asn
            18275   18280   18285
Val Gly Gly Thr Lys Ser Ile Pro Ile Thr Val Lys Val Leu Asp Arg
            18290   18295   18300   1
Pro Gly Ser Pro Glu Gly Pro Leu Lys Val Thr Gly Val Thr Ala Glu
8305   18310   18315   18320
Lys Cys Tyr Leu Ala Trp Asn Pro Pro Leu Gln Asp Gly Gly Ala Asn
            18325   18330   18335
Ile Ser His Tyr Ile Ile Glu Lys Arg Glu Thr Ser Arg Leu Ser Trp
            18340   18345   18350
Thr Gln Val Ser Thr Glu Val Gln Ala Leu Asn Tyr Lys Val Thr Lys
            18355   18360   18365
Leu Leu Pro Gly Asn Glu Tyr Ile Phe Arg Val Met Ala Val Asn Lys
            18370   18375   18380   1
Tyr Gly Ile Gly Glu Pro Leu Glu Ser Gly Pro Val Thr Ala Cys Asn
8385   18390   18395   18400
Pro Tyr Lys Pro Pro Gly Pro Pro Ser Thr Pro Glu Val Ser Ala Ile
            18405   18410   18415
Thr Lys Asp Ser Met Val Val Thr Trp Ala Arg Pro Val Asp Asp Gly
            18420   18425   18430
Gly Thr Glu Ile Glu Gly Tyr Ile Leu Glu Lys Arg Asp Lys Glu Gly
            18435   18440   18445
Val Arg Trp Thr Lys Cys Asn Lys Lys Thr Leu Thr Asp Leu Arg Leu
            18450   18455   18460   1
Arg Val Thr Gly Leu Thr Glu Gly His Ser Tyr Glu Phe Arg Val Ala
8465   18470   18475   18480
Ala Glu Asn Ala Ala Gly Val Gly Glu Pro Ser Glu Pro Ser Val Phe
            18485   18490   18495
Tyr Arg Ala Cys Asp Ala Leu Tyr Pro Pro Gly Pro Pro Ser Asn Pro
            18500   18505   18510
Lys Val Thr Asp Thr Ser Arg Ser Ser Val Ser Leu Ala Trp Ser Lys
            18515   18520   18525
Pro Ile Tyr Asp Gly Gly Ala Pro Val Lys Gly Tyr Val Val Glu Val
            18530   18535   18540   1
Lys Glu Ala Ala Ala Asp Glu Trp Thr Thr Cys Thr Pro Pro Thr Gly
8545   18550   18555   18560
Leu Gln Gly Lys Gln Phe Thr Val Thr Lys Leu Lys Glu Asn Thr Glu
            18565   18570   18575

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Tyr Asn Phe Arg Ile Cys Ala Ile Asn Ser Glu Gly Val Gly Glu Pro
        18580               18585               18590
Ala Thr Leu Pro Gly Ser Val Val Ala Gln Glu Arg Ile Glu Pro Pro
        18595               18600               18605
Glu Ile Glu Leu Asp Ala Asp Leu Arg Lys Val Val Val Leu Arg Ala
        18610               18615               18620            1
Ser Ala Thr Leu Arg Leu Phe Val Thr Ile Lys Gly Arg Pro Glu Pro
8625            18630               18635               18640
Glu Val Lys Trp Glu Lys Ala Glu Gly Ile Leu Thr Asp Arg Ala Gln
        18645               18650               18655
Ile Glu Val Thr Ser Ser Phe Thr Met Leu Val Ile Asp Asn Val Thr
        18660               18665               18670
Arg Phe Asp Ser Gly Arg Tyr Asn Leu Thr Leu Glu Asn Asn Ser Gly
        18675               18680               18685
Ser Lys Thr Ala Phe Val Asn Val Arg Val Leu Asp Ser Pro Ser Ala
        18690               18695               18700            1
Pro Val Asn Leu Thr Ile Arg Glu Val Lys Lys Asp Ser Val Thr Leu
8705            18710               18715               18720
Ser Trp Glu Pro Pro Leu Ile Asp Gly Gly Ala Lys Ile Thr Asn Tyr
        18725               18730               18735
Ile Val Glu Lys Arg Glu Thr Thr Arg Lys Ala Tyr Ala Thr Ile Thr
        18740               18745               18750
Asn Asn Cys Thr Lys Thr Thr Phe Arg Ile Glu Asn Leu Gln Glu Gly
        18755               18760               18765
Cys Ser Tyr Tyr Phe Arg Val Leu Ala Ser Asn Glu Tyr Gly Ile Gly
        18770               18775               18780            1
Leu Pro Ala Glu Thr Thr Glu Pro Val Lys Val Ser Glu Pro Pro Leu
8785            18790               18795               18800
Pro Pro Gly Arg Val Thr Leu Val Asp Val Thr Arg Asn Thr Ala Thr
        18805               18810               18815
Ile Lys Trp Glu Lys Pro Glu Ser Asp Gly Gly Ser Lys Ile Thr Gly
        18820               18825               18830
Tyr Val Val Glu Met Gln Thr Lys Gly Ser Glu Lys Trp Ser Thr Cys
        18835               18840               18845
Thr Gln Val Lys Thr Leu Glu Ala Thr Ile Ser Gly Leu Thr Ala Gly
        18850               18855               18860            1
Glu Glu Tyr Val Phe Arg Val Ala Ala Val Asn Glu Lys Gly Arg Ser
8865            18870               18875               18880
Asp Pro Arg Gln Leu Gly Val Pro Val Ile Ala Arg Asp Ile Glu Ile
        18885               18890               18895
Lys Pro Ser Val Glu Leu Pro Phe His Thr Phe Asn Val Lys Ala Arg
        18900               18905               18910
Glu Gln Leu Lys Ile Asp Val Pro Phe Lys Gly Arg Pro Gln Ala Thr
        18915               18920               18925
Val Asn Trp Arg Lys Asp Gly Gln Thr Leu Lys Glu Thr Thr Arg Val
        18930               18935               18940            1
Asn Val Ser Ser Ser Lys Thr Val Thr Ser Leu Ser Ile Lys Glu Ala
8945            18950               18955               18960
Ser Lys Glu Asp Val Gly Thr Tyr Glu Leu Cys Val Ser Asn Ser Ala
        18965               18970               18975
Gly Ser Ile Thr Val Pro Ile Thr Ile Ile Val Leu Asp Arg Pro Gly
        18980               18985               18990
Pro Pro Gly Pro Ile Arg Ile Asp Glu Val Ser Cys Asp Ser Ile Thr
        18995               19000               19005
Ile Ser Trp Asn Pro Pro Glu Tyr Asp Gly Gly Cys Gln Ile Ser Asn
        19010               19015               19020            1
Tyr Ile Val Glu Lys Lys Glu Thr Thr Ser Thr Thr Trp His Ile Val
9025            19030               19035               19040
Ser Gln Ala Val Ala Arg Thr Ser Ile Lys Ile Val Arg Leu Thr Thr
        19045               19050               19055
Gly Ser Glu Tyr Gln Phe Arg Val Cys Ala Glu Asn Arg Tyr Gly Lys
        19060               19065               19070
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Ser Ser Tyr Ser Glu Ser Ser Ala Val Val Ala Glu Tyr Pro Phe Ser
      19075              19080              19085
Pro Pro Gly Pro Pro Gly Thr Pro Lys Val Val His Ala Thr Lys Ser
      19090              19095              19100                    1
Thr Met Leu Val Thr Trp Gln Val Pro Val Asn Asp Gly Gly Ser Arg
9105              19110              19115                  19120
Val Ile Gly Tyr His Leu Glu Tyr Lys Glu Arg Ser Ser Ile Leu Trp
      19125              19130              19135
Ser Lys Ala Asn Lys Ile Leu Ile Ala Asp Thr Gln Val Lys Val Ser
      19140              19145              19150
Gly Leu Asp Glu Gly Leu Met Tyr Glu Tyr Arg Val Tyr Ala Glu Asn
      19155              19160              19165
Ile Ala Gly Ile Gly Lys Cys Ser Lys Ser Cys Glu Pro Val Pro Ala
      19170              19175              19180                    1
Arg Asp Pro Cys Asp Pro Pro Gly Gln Pro Glu Val Thr Asn Ile Thr
9185              19190              19195                  19200
Arg Lys Ser Val Ser Leu Lys Trp Ser Lys Pro His Tyr Asp Gly Gly
              19205              19210              19215
Ala Lys Ile Thr Gly Tyr Ile Val Glu Arg Arg Glu Leu Pro Asp Gly
      19220              19225              19230
Arg Trp Leu Lys Cys Asn Tyr Thr Asn Ile Gln Glu Thr Tyr Phe Glu
      19235              19240              19245
Val Thr Glu Leu Thr Glu Asp Gln Arg Tyr Glu Phe Arg Val Phe Ala
      19250              19255              19260                    1
Arg Asn Ala Ala Asp Ser Val Ser Glu Pro Ser Glu Ser Thr Gly Pro
9265              19270              19275                  19280
Ile Ile Val Lys Asp Asp Val Glu Pro Pro Arg Val Met Met Asp Val
              19285              19290              19295
Lys Phe Arg Asp Val Ile Val Val Lys Ala Gly Glu Val Leu Lys Ile
      19300              19305              19310
Asn Ala Asp Ile Ala Gly Arg Pro Leu Pro Val Ile Ser Trp Ala Lys
      19315              19320              19325
Asp Gly Ile Glu Ile Glu Glu Arg Ala Arg Thr Glu Ile Ile Ser Thr
      19330              19335              19340                    1
Asp Asn His Thr Leu Leu Thr Val Lys Asp Cys Ile Arg Arg Asp Thr
9345              19350              19355                  19360
Gly Gln Tyr Val Leu Thr Leu Lys Asn Val Ala Gly Thr Arg Ser Val
              19365              19370              19375
Ala Val Asn Cys Lys Val Leu Asp Lys Pro Gly Pro Pro Ala Gly Pro
      19380              19385              19390
Leu Glu Ile Asn Gly Leu Thr Ala Glu Lys Cys Ser Leu Ser Trp Gly
      19395              19400              19405
Arg Pro Gln Glu Asp Gly Gly Ala Asp Ile Asp Tyr Tyr His Arg Lys
      19410              19415              19420                    1
Lys Arg Glu Thr Ser His Leu Ala Trp Thr Ile Cys Glu Gly Glu Leu
9425              19430              19435                  19440
Gln Met Thr Ser Cys Lys Val Thr Lys Leu Leu Lys Gly Asn Glu Tyr
              19445              19450              19455
Ile Phe Arg Val Thr Gly Val Asn Lys Tyr Gly Val Gly Glu Pro Leu
      19460              19465              19470
Glu Ser Val Ala Ile Lys Ala Leu Asp Pro Phe Thr Val Pro Ser Pro
      19475              19480              19485
Pro Thr Ser Leu Glu Ile Thr Ser Val Thr Lys Glu Ser Met Thr Leu
      19490              19495              19500                    1
Cys Trp Ser Arg Pro Glu Ser Asp Gly Gly Ser Glu Ile Ser Gly Tyr
9505              19510              19515                  19520
Ile Ile Glu Arg Arg Glu Lys Asn Ser Leu Arg Trp Val Arg Val Asn
              19525              19530              19535
Lys Lys Pro Val Tyr Asp Leu Arg Val Lys Ser Thr Gly Leu Arg Glu
      19540              19545              19550
Gly Cys Glu Tyr Glu Tyr Arg Val Tyr Ala Glu Asn Ala Ala Gly Leu
      19555              19560              19565
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Ser Leu Pro Ser Glu Thr Ser Pro Leu Ile Arg Ala Glu Asp Pro Val
   19570   19575   19580   1
Phe Leu Pro Ser Pro Pro Ser Lys Pro Lys Ile Val Asp Ser Gly Lys
9585   19590   19595   19600
Thr Thr Ile Thr Ile Ala Trp Val Lys Pro Leu Phe Asp Gly Gly Ala
        19605   19610   .   19615
Pro Ile Thr Gly Tyr Thr Val Glu Tyr Lys Lys Ser Asp Asp Thr Asp
        19620   19625   19630
Trp Lys Thr Ser Ile Gln Ser Leu Arg Gly Thr Glu Tyr Thr Ile Ser
     19635   19640   19645
Gly Leu Thr Thr Gly Ala Glu Tyr Val Phe Arg Val Lys Ser Val Asn
    19650   19655   19660   1
Lys Val Gly Ala Ser Asp Pro Ser Asp Ser Ser Asp Pro Gln Ile Ala
9665   19670   19675   19680
Lys Glu Arg Glu Glu Glu Pro Leu Phe Asp Ile Asp Ser Glu Met Arg
        19685   19690   19695
Lys Thr Leu Ile Val Lys Ala Gly Ala Ser Phe Thr Met Thr Val Pro
        19700   19705   19710
Phe Arg Gly Arg Pro Val Pro Asn Val Leu Trp Ser Lys Pro Asp Thr
    19715   19720   19725
Asp Leu Arg Thr Arg Ala Tyr Val Asp Thr Thr Asp Ser Arg Thr Ser
    19730   19735   19740   1
Leu Thr Ile Glu Asn Ala Asn Arg Asn Asp Ser Gly Lys Tyr Thr Leu
9745   19750   19755   19760
Thr Ile Gln Asn Val Leu Ser Ala Ala Ser Leu Thr Leu Val Val Lys
        19765   19770   19775
Val Leu Asp Thr Pro Gly Pro Pro Thr Asn Ile Thr Val Gln Asp Val
        19780   19785   19790
Thr Lys Glu Ser Ala Val Leu Ser Trp Asp Val Pro Glu Asn Asp Gly
     19795   19800   .   19805
Gly Ala Pro Val Lys Asn Tyr His Ile Glu Lys Arg Glu Ala Ser Lys
    19810   19815   19820   1
Lys Ala Trp Val Ser Val Thr Asn Asn Cys Asn Arg Leu Ser Tyr Lys
9825   19830   19835   19840
Val Thr Asn Leu Gln Glu Gly Ala Ile Tyr Tyr Phe Arg Val Ser Gly
        19845   19850   19855
Glu Asn Glu Phe Gly Val Gly Ile Pro Ala Glu Thr Lys Glu Gly Val
    19860   19865   19870
Lys Ile Thr Glu Lys Pro Ser Pro Pro Glu Lys Leu Gly Val Thr Ser
    19875   19880   19885
Ile Ser Lys Asp Ser Val Ser Leu Thr Trp Leu Lys Pro Glu His Asp
    19890   19895   19900   1
Gly Gly Ser Arg Ile Val His Tyr Val Val Glu Ala Leu Glu Lys Gly
9905   19910   19915   19920
Gln Lys Asn Trp Val Lys Cys Ala Val Ala Lys Ser Thr His His Val
        19925   19930   19935
Val Ser Gly Leu Arg Glu Asn Ser Glu Tyr Phe Phe Arg Val Phe Ala
        19940   19945   19950
Glu Asn Gln Ala Gly Leu Ser Asp Pro Arg Glu Leu Leu Leu Pro Val
    19955   19960   19965
Leu Ile Lys Glu Gln Leu Glu Pro Pro Glu Ile Asp Met Lys Asn Phe
    19970   19975   19980   1
Pro Ser His Thr Val Tyr Val Arg Ala Gly Ser Asn Leu Lys Val Asp
9985   19990   19995   20000
Ile Pro Ile Ser Gly Lys Pro Leu Pro Lys Val Thr Leu Ser Arg Asp
        20005   20010   20015
Gly Val Pro Leu Lys Ala Thr Met Arg Phe Asn Thr Glu Ile Thr Ala
        20020   20025   20030
Glu Asn Leu Thr Ile Asn Leu Lys Glu Ser Val Thr Ala Asp Ala Gly
    20035   20040   20045
Arg Tyr Glu Ile Thr Ala Ala Asn Ser Ser Gly Thr Thr Lys Ala Phe
    20050   20055   20060   2

Ile Asn Ile Val Val Leu Asp Arg Pro Gly Pro Pro Thr Gly Pro Val
0065   20070   20075   20080
Val Ile Ser Asp Ile Thr Glu Glu Ser Val Thr Leu Lys Trp Glu Pro
                20085   20090   20095
Pro Lys Tyr Asp Gly Gly Ser Gln Val Thr Asn Tyr Ile Leu Leu Lys
            20100   20105   20110
Arg Glu Thr Ser Thr Ala Val Trp Thr Glu Val Ser Ala Thr Val Ala
        20115   20120   20125
Arg Thr Met Met Lys Val Met Lys Leu Thr Thr Gly Glu Glu Tyr Gln
    20130   20135   20140   2
Phe Arg Ile Lys Ala Glu Asn Arg Phe Gly Ile Ser Asp His Ile Asp
0145   20150   20155   20160
Ser Ala Cys Val Thr Val Lys Leu Pro Tyr Thr Thr Pro Gly Pro Pro
                20165   20170   20175
Ser Thr Pro Trp Val Thr Asn Val Thr Arg Glu Ser Ile Thr Val Gly
            20180   20185   20190
Trp His Glu Pro Val Ser Asn Gly Gly Ser Ala Val Val Gly Tyr His
            20195   20200   20205
Leu Glu Met Lys Asp Arg Asn Ser Ile Leu Trp Gln Lys Ala Asn Lys
        20210   20215   20220   2
Leu Val Ile Arg Thr Thr His Phe Lys Val Thr Thr Ile Ser Ala Gly
0225   20230   20235   20240
Leu Ile Tyr Glu Phe Arg Val Tyr Ala Glu Asn Ala Ala Gly Val Gly
            20245   20250   20255
Lys Pro Ser His Pro Ser Glu Pro Val Leu Ala Ile Asp Ala Cys Glu
            20260   20265   20270
Pro Pro Arg Asn Val Arg Ile Thr Asp Ile Ser Lys Asn Ser Val Ser
        20275   20280   20285
Leu Ser Trp Gln Gln Pro Ala Phe Asp Gly Gly Ser Lys Ile Thr Gly
    20290   20295   20300   2
Tyr Ile Val Glu Arg Arg Asp Leu Pro Asp Gly Arg Trp Thr Lys Ala
0305   20310   20315   20320
Ser Phe Thr Asn Val Thr Glu Thr Gln Phe Thr Ile Ser Gly Leu Thr
                20325   20330   20335
Gln Asn Ser Gln Tyr Glu Phe Arg Val Phe Ala Arg Asn Ala Val Gly
            20340   20345   20350
Ser Ile Ser Asn Pro Ser Glu Val Val Gly Pro Ile Thr Cys Ile Asp
        20355   20360   20365
Ser Tyr Gly Gly Pro Val Ile Asp Leu Pro Leu Glu Tyr Thr Glu Val
    20370   20375   20380   2
Val Lys Tyr Arg Ala Gly Thr Ser Val Lys Leu Arg Ala Gly Ile Ser
0385   20390   20395   20400
Gly Lys Pro Ala Pro Thr Ile Glu Trp Tyr Lys Asp Asp Lys Glu Leu
            20405   20410   20415
Gln Thr Asn Ala Leu Val Cys Val Glu Asn Thr Thr Asp Leu Ala Ser
        20420   20425   20430
Ile Leu Ile Lys Asp Ala Asp Arg Leu Asn Ser Gly Cys Tyr Glu Leu
    20435   .   20440   20445
Lys Leu Arg Asn Ala Met Ala Ser Ala Ser Ala Thr Ile Arg Val Gln
    20450   20455   20460   2
Ile Leu Asp Lys Pro Gly Pro Pro Gly Gly Pro Ile Glu Phe Lys Thr
0465   20470   20475   20480
Val Thr Ala Glu Lys Ile Thr Leu Leu Trp Arg Pro Pro Ala Asp Asp
                20485   20490   20495
Gly Gly Ala Lys Ile Thr His Tyr Ile Val Glu Lys Arg Glu Thr Ser
            20500   20505   20510
Arg Val Val Trp Ser Met Val Ser Glu His Leu Glu Glu Cys Ile Ile
        20515   20520   20525
Thr Thr Thr Lys Ile Ile Lys Gly Asn Glu Tyr Ile Phe Arg Val Arg
    20530   20535   20540   2
Ala Val Asn Lys Tyr Gly Ile Gly Glu Pro Leu Glu Ser Asp Ser Val
0545   20550   20555   20560

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Val Ala Lys Asn Ala Phe Val Thr Pro Gly Pro Pro Gly Ile Pro Glu
          20565              20570              20575
Val Thr Lys Ile Thr Lys Asn Ser Met Thr Val Val Trp Ser Arg Pro
          20580              20585              20590
Ile Ala Asp Gly Gly Ser Asp Ile Ser Gly Tyr Phe Leu Glu Lys Arg
       20595              20600              20605
Asp Lys Lys Ser Leu Gly Trp Phe Lys Val Leu Lys Glu Thr Ile Arg
    20610              20615              20620              2
Asp Thr Arg Gln Lys Val Thr Gly Leu Thr Glu Asn Ser Asp Tyr Gln
0625              20630              20635              20640
Tyr Arg Val Cys Ala Val Asn Ala Ala Gly Gln Gly Pro Phe Ser Glu
          20645              20650              20655
Pro Ser Glu Phe Tyr Lys Ala Ala Asp Pro Ile Asp Pro Pro Gly Pro
          20660              20665              20670
Pro Ala Lys Ile Arg Ile Ala Asp Ser Thr Lys Ser Ser Ile Thr Leu
       20675              20680              20685
Gly Trp Ser Lys Pro Val Tyr Asp Gly Gly Ser Ala Val Thr Gly Tyr
    20690              20695              20700              2
Val Val Glu Ile Arg Gln Gly Glu Glu Glu Trp Thr Thr Val Ser
0705              20710              20715              20720
Thr Lys Gly Glu Val Arg Thr Thr Glu Tyr Val Val Ser Asn Leu Lys
          20725              20730              20735
Pro Gly Val Asn Tyr Tyr Phe Arg Val Ser Ala Val Asn Cys Ala Gly
       20740              20745              20750
Gln Gly Glu Pro Ile Glu Met Asn Glu Pro Val Gln Ala Lys Asp Ile
       20755              20760              20765
Leu Glu Ala Pro Glu Ile Asp Leu Asp Val Ala Leu Arg Thr Ser Val
    20770              20775              20780              2
Ile Ala Lys Ala Gly Glu Asp Val Gln Val Leu Ile Pro Phe Lys Gly
0785              20790              20795              20800
Arg Pro Pro Pro Thr Val Thr Trp Arg Lys Asp Glu Lys Asn Leu Gly
          20805              20810              20815
Ser Asp Ala Arg Tyr Ser Ile Glu Asn Thr Asp Ser Ser Ser Leu Leu
       20820              20825              20830
Thr Ile Pro Gln Val Thr Arg Asn Asp Thr Gly Lys Tyr Ile Leu Thr
    20835              20840              20845
Ile Glu Asn Gly Val Gly Glu Pro Lys Ser Ser Thr Val Ser Val Lys
    20850              20855              20860              2
Val Leu Asp Thr Pro Ala Ala Cys Gln Lys Leu Gln Val Lys His Val
0865              20870              20875              20880
Ser Arg Gly Thr Val Thr Leu Leu Trp Asp Pro Pro Leu Ile Asp Gly
          20885              20890              20895
Gly Ser Pro Ile Ile Asn Tyr Val Ile Glu Lys Arg Asp Ala Thr Lys
       20900              20905              20910
Arg Thr Trp Ser Val Val Ser His Lys Cys Ser Ser Thr Ser Phe Lys
       20915              20920              20925
Leu Ile Asp Leu Ser Glu Lys Thr Pro Phe Phe Phe Arg Val Leu Ala
    20930              20935              20940              2
Glu Asn Glu Ile Gly Ile Gly Glu Pro Cys Glu Thr Thr Glu Pro Val
0945              20950              20955              20960
Lys Ala Ala Glu Val Pro Ala Pro Ile Arg Asp Leu Ser Met Lys Asp
          20965              20970              20975
Ser Thr Lys Thr Ser Val Ile Leu Ser Trp Thr Lys Pro Asp Phe Asp
       20980              20985              20990
Gly Gly Ser Val Ile Thr Glu Tyr Val Val Glu Arg Lys Gly Lys Gly
    20995              21000              21005
Glu Gln Thr Trp Ser His Ala Gly Ile Ser Lys Thr Cys Glu Ile Glu
    21010              21015              21020              2
Val Ser Gln Leu Lys Glu Gln Ser Val Leu Glu Phe Arg Val Phe Ala
1025              21030              21035              21040
Lys Asn Glu Lys Gly Leu Ser Asp Pro Val Thr Ile Gly Pro Ile Thr
          21045              21050              21055
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Val Lys Glu Leu Ile Ile Thr Pro Glu Val Asp Leu Ser Asp Ile Pro
         21060              21065              21070
Gly Ala Gln Val Thr Val Arg Ile Gly His Asn Val His Leu Glu Leu
      21075              21080              21085
Pro Tyr Lys Gly Lys Pro Lys Pro Ser Ile Ser Trp Leu Lys Asp Gly
    21090              21095              21100              2
Leu Pro Leu Lys Glu Ser Glu Phe Val Arg Phe Ser Lys Thr Glu Asn
1105              21110              21115              21120
Lys Ile Thr Leu Ser Ile Lys Asn Ala Lys Lys Glu His Gly Gly Lys
         21125              21130              21135
Tyr Thr Val Ile Leu Asp Asn Ala Val Cys Arg Ile Ala Val Pro Ile
      21140              21145              21150
Thr Val Ile Thr Leu Gly Pro Pro Ser Lys Pro Lys Gly Pro Ile Arg
      21155              21160              21165
Phe Asp Glu Ile Lys Ala Asp Ser Val Ile Leu Ser Trp Asp Val Pro
    21170              21175              21180              2
Glu Asp Asn Gly Gly Gly Glu Ile Thr Cys Tyr Ser Ile Glu Lys Arg
1185              21190              21195              21200
Glu Thr Ser Gln Thr Asn Trp Lys Met Val Cys Ser Ser Val Ala Arg
         21205              21210              21215
Thr Thr Phe Lys Val Pro Asn Leu Val Lys Asp Ala Glu Tyr Gln Phe
      21220              21225              21230
Arg Val Arg Ala Glu Asn Arg Tyr Gly Val Ser Gln Pro Leu Val Ser
      21235              21240              21245
Ser Ile Ile Val Ala Lys His Gln Phe Arg Ile Pro Gly Pro Pro Gly
    21250              21255              21260              2
Lys Pro Val Ile Tyr Asn Val Thr Ser Asp Gly Met Ser Leu Thr Trp
1265              21270              21275              21280
Asp Ala Pro Val Tyr Asp Gly Gly Ser Glu Val Thr Gly Phe His Val
         21285              21290              21295
Glu Lys Lys Glu Arg Asn Ser Ile Leu Trp Gln Lys Val Asn Thr Ser
      21300              21305              21310
Pro Ile Ser Gly Arg Glu Tyr Arg Ala Thr Gly Leu Val Glu Gly Leu
    21315              21320              21325
Asp Tyr Gln Phe Arg Val Tyr Ala Glu Asn Ser Ala Gly Leu Ser Ser
    21330              21335              21340              2
Pro Ser Asp Pro Ser Lys Phe Thr Leu Ala Val Ser Pro Val Asp Pro
1345              21350              21355              21360
Pro Gly Thr Pro Asp Tyr Ile Asp Val Thr Arg Glu Thr Ile Thr Leu
         21365              21370              21375
Lys Trp Asn Pro Pro Leu Arg Asp Gly Gly Ser Lys Ile Val Gly Tyr
      21380              21385              21390
Ser Ile Glu Lys Arg Gln Gly Asn Glu Arg Trp Val Arg Cys Asn Phe
      21395              21400              21405
Thr Asp Val Ser Glu Cys Gln Tyr Thr Val Thr Gly Leu Ser Pro Gly
    21410              21415              21420              2
Asp Arg Tyr Glu Phe Arg Ile Ile Ala Arg Asn Ala Val Gly Thr Ile
1425              21430              21435              21440
Ser Pro Pro Ser Gln Ser Ser Gly Ile Ile Met Thr Arg Asp Glu Asn
         21445              21450              21455
Val Pro Pro Ile Val Glu Phe Gly Pro Glu Tyr Phe Asp Gly Leu Ile
      21460              21465              21470
Ile Lys Ser Gly Glu Ser Leu Arg Ile Lys Ala Leu Val Gln Gly Arg
    21475              21480              21485
Pro Val Pro Arg Val Thr Trp Phe Lys Asp Gly Val Glu Ile Glu Lys
    21490              21495              21500              2
Arg Met Asn Met Glu Ile Thr Asn Val Leu Gly Ser Thr Ser Leu Phe
1505              21510              21515              21520
Val Arg Asp Ala Thr Arg Asp His Arg Gly Val Tyr Thr Val Glu Ala
         21525              21530              21535
Lys Asn Ala Ser Gly Ser Ala Lys Ala Glu Ile Lys Val Lys Val Gln
      21540              21545              21550
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Asp Thr Pro Gly Lys Val Val Gly Pro Ile Arg Phe Thr Asn Ile Thr
    21555               21560               21565
Gly Glu Lys Met Thr Leu Trp Trp Asp Ala Pro Leu Asn Asp Gly Cys
    21570               21575               21580           2
Ala Pro Ile Thr His Tyr Ile Ile Glu Lys Arg Glu Thr Ser Arg Leu
1585               21590               21595               21600
Ala Trp Ala Leu Ile Glu Asp Lys Cys Glu Ala Gln Ser Tyr Thr Ala
            21605               21610               21615
Ile Lys Leu Ile Asn Gly Asn Glu Tyr Gln Phe Arg Val Ser Ala Val
            21620               21625               21630
Asn Lys Phe Gly Val Gly Arg Pro Leu Asp Ser Asp Pro Val Val Ala
    21635               21640               21645
Gln Ile Gln Tyr Thr Val Pro Asp Ala Pro Gly Ile Pro Glu Pro Ser
    21650               21655               21660           2
Asn Ile Thr Gly Asn Ser Ile Thr Leu Thr Trp Ala Arg Pro Glu Ser
1665               21670               21675               21680
Asp Gly Gly Ser Glu Ile Gln Gln Tyr Ile Leu Glu Arg Arg Glu Lys
            21685               21690               21695
Lys Ser Thr Arg Trp Val Lys Val Ile Ser Lys Arg Pro Ile Ser Glu
            21700               21705               21710
Thr Arg Phe Lys Val Thr Gly Leu Thr Glu Gly Asn Glu Tyr Glu Phe
            21715               21720               21725
His Val Met Ala Glu Asn Ala Ala Gly Val Gly Pro Ala Ser Gly Ile
    21730               21735               21740           2
Ser Arg Leu Ile Lys Cys Arg Glu Pro Val Asn Pro Pro Gly Pro Pro
1745               21750               21755               21760
Thr Val Val Lys Val Thr Asp Thr Ser Lys Thr Thr Val Ser Leu Glu
            21765               21770               21775
Trp Ser Lys Pro Val Phe Asp Gly Gly Met Glu Ile Ile Gly Tyr Ile
            21780               21785               21790
Ile Glu Met Cys Lys Thr Asp Leu Gly Asp Trp His Lys Val Asn Ala
        21795               21800               21805
Glu Ala Cys Val Lys Thr Arg Tyr Thr Val Thr Asp Leu Gln Ala Gly
    21810               21815               21820           2
Glu Glu Tyr Lys Phe Arg Val Ser Ala Ile Asn Gly Ala Gly Lys Gly
1825               21830               21835               21840
Asp Ser Cys Glu Val Thr Gly Thr Ile Lys Ala Val Asp Arg Leu Thr
            21845               21850               21855
Ala Pro Glu Leu Asp Ile Asp Ala Asn Phe Lys Gln Thr His Val Val
            21860               21865               21870
Arg Ala Gly Ala Ser Ile Arg Leu Phe Ile Ala Tyr Gln Gly Arg Pro
    21875               21880               21885
Thr Pro Thr Ala Val Trp Ser Lys Pro Asp Ser Asn Leu Ser Leu Arg
    21890               21895               21900           2
Ala Asp Ile His Thr Thr Asp Ser Phe Ser Thr Leu Thr Val Glu Asn
1905               21910               21915               21920
Cys Asn Arg Asn Asp Ala Gly Lys Tyr Thr Leu Thr Val Glu Asn Asn
            21925               21930               21935
Ser Gly Ser Lys Ser Ile Thr Phe Thr Val Lys Val Leu Asp Thr Pro
            21940               21945               21950
Gly Pro Pro Gly Pro Ile Thr Phe Lys Asp Val Thr Arg Gly Ser Ala
        21955               21960               21965
Thr Leu Met Trp Asp Ala Pro Leu Leu Asp Gly Gly Ala Arg Ile His
    21970               21975               21980           2
His Tyr Val Val Glu Lys Arg Glu Ala Ser Arg Arg Ser Trp Gln Val
1985               21990               21995               22000
Ile Ser Glu Lys Cys Thr Arg Gln Ile Phe Lys Val Asn Asp Leu Ala
            22005               22010               22015
Glu Gly Val Pro Tyr Tyr Phe Arg Val Ser Ala Val Asn Glu Tyr Gly
        22020               22025               22030
Val Gly Glu Pro Tyr Glu Met Pro Glu Pro Ile Val Ala Thr Glu Gln
    22035               22040               22045
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Pro Ala Pro Pro Arg Arg Leu Asp Val Val Asp Thr Ser Lys Ser Ser
    22050               22055               22060               2
Ala Val Leu Ala Trp Leu Lys Pro Asp His Asp Gly Gly Ser Arg Ile
2065                22070               22075               22080
Thr Gly Tyr Leu Leu Glu Met Arg Gln Lys Gly Ser Asp Leu Trp Val
                22085               22090               22095
Glu Ala Gly His Thr Lys Gln Leu Thr Phe Thr Val Glu Arg Leu Val
                22100               22105               22110
Glu Lys Thr Glu Tyr Glu Phe Arg Val Lys Ala Lys Asn Asp Ala Gly
        22115               22120               22125
Tyr Ser Glu Pro Arg Glu Ala Phe Ser Ser Val Ile Ile Lys Glu Pro
        22130               22135               22140               2
Gln Ile Glu Pro Thr Ala Asp Leu Thr Gly Ile Thr Asn Gln Leu Ile
2145                22150               22155               22160
Thr Cys Lys Ala Gly Ser Pro Phe Thr Ile Asp Val Pro Ile Ser Gly
                22165               22170               22175
Arg Pro Ala Pro Lys Val Thr Trp Lys Leu Glu Glu Met Arg Leu Lys
                22180               22185               22190
Glu Thr Asp Arg Val Ser Ile Thr Thr Thr Lys Asp Arg Thr Thr Leu
        22195               22200               22205
Thr Val Lys Asp Ser Met Arg Gly Asp Ser Gly Arg Tyr Phe Leu Thr
    22210               22215               22220               2
Leu Glu Asn Thr Ala Gly Val Lys Thr Phe Ser Val Thr Val Val Val
2225                22230               22235               22240
Ile Gly Arg Pro Gly Pro Val Thr Gly Pro Ile Glu Val Ser Ser Val
                22245               22250               22255
Ser Ala Glu Ser Cys Val Leu Ser Trp Gly Glu Pro Lys Asp Gly Gly
        22260               22265               22270
Gly Thr Glu Ile Thr Asn Tyr Ile Val Glu Lys Arg Glu Ser Gly Thr
        22275               22280               22285
Thr Ala Trp Gln Leu Val Asn Ser Ser Val Lys Arg Thr Gln Ile Lys
        22290               22295               22300               2
Val Thr His Leu Thr Lys Tyr Met Glu Tyr Ser Phe Arg Val Ser Ser
2305                22310               22315               22320
Glu Asn Arg Phe Gly Val Ser Lys Pro Leu Glu Ser Ala Pro Ile Ile
                22325               22330               22335
Ala Glu His Pro Phe Val Pro Pro Ser Ala Pro Thr Arg Pro Glu Val
            22340               22345               22350
Tyr His Val Ser Ala Asn Ala Met Ser Ile Arg Trp Glu Glu Pro Tyr
        22355               22360               22365
His Asp Gly Gly Ser Lys Ile Ile Gly Tyr Trp Val Glu Lys Lys Glu
    22370               22375               22380               2
Arg Asn Thr Ile Leu Trp Val Lys Glu Asn Lys Val Pro Cys Leu Glu
2385                22390               22395               22400
Cys Asn Tyr Lys Val Thr Gly Leu Val Glu Gly Leu Glu Tyr Gln Phe
            22405               22410               22415
Arg Thr Tyr Ala Leu Asn Ala Ala Gly Val Ser Lys Ala Ser Glu Ala
        22420               22425               22430
Ser Arg Pro Ile Met Ala Gln Asn Pro Val Asp Ala Pro Gly Arg Pro
        22435               22440               22445
Glu Val Thr Asp Val Thr Arg Ser Thr Val Ser Leu Ile Trp Ser Ala
    22450               22455               22460               2
Pro Ala Tyr Asp Gly Gly Ser Lys Val Val Gly Tyr Ile Ile Glu Arg
2465                22470               22475               22480
Lys Pro Val Ser Glu Val Gly Asp Gly Arg Trp Leu Lys Cys Asn Tyr
            22485               22490               22495
Thr Ile Val Ser Asp Asn Phe Phe Thr Val Thr Ala Leu Ser Glu Gly
            22500               22505               22510
Asp Thr Tyr Glu Phe Arg Val Leu Ala Lys Asn Ala Ala Gly Val Ile
        22515               22520               22525
Ser Lys Gly Ser Glu Ser Thr Gly Pro Val Thr Cys Arg Asp Glu Tyr
    22530               22535               22540               2
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Ala Pro Pro Lys Ala Glu Leu Asp Ala Arg Leu His Gly Asp Leu Val
2545              22550              22555              22560
Thr Ile Arg Ala Gly Ser Asp Leu Val Leu Asp Ala Ala Val Gly Gly
          22565              22570              22575
Lys Pro Glu Pro Lys Ile Ile Trp Thr Lys Gly Asp Lys Glu Leu Asp
          22580              22585              22590
Leu Cys Glu Lys Val Ser Leu Gln Tyr Thr Gly Lys Arg Ala Thr Ala
     22595              22600              22605
Val Ile Lys Phe Cys Asp Arg Ser Asp Ser Gly Lys Tyr Thr Leu Thr
     22610              22615              22620              2
Val Lys Asn Ala Ser Gly Thr Lys Ala Val Ser Val Met Val Lys Val
2625              22630              22635              22640
Leu Asp Ser Pro Gly Pro Cys Gly Lys Leu Thr Val Ser Arg Val Thr
          22645              22650              22655
Gln Glu Lys Cys Thr Leu Ala Trp Ser Leu Pro Gln Glu Asp Gly Gly
     22660              22665              22670
Ala Glu Ile Thr His Tyr Ile Val Glu Arg Arg Glu Thr Ser Arg Leu
     22675              22680              22685
Asn Trp Val Ile Val Glu Gly Glu Cys Pro Thr Leu Ser Tyr Val Val
     22690              22695              22700              2
Thr Arg Leu Ile Lys Asn Asn Glu Tyr Ile Phe Arg Val Arg Ala Val
2705              22710              22715              22720
Asn Lys Tyr Gly Pro Gly Val Pro Val Glu Ser Glu Pro Ile Val Ala
          22725              22730              22735
Arg Asn Ser Phe Thr Ile Pro Ser Pro Pro Gly Ile Pro Glu Glu Val
          22740              22745              22750
Gly Thr Gly Lys Glu His Ile Ile Ile Gln Trp Thr Lys Pro Glu Ser
     22755              22760              22765
Asp Gly Gly Asn Glu Ile Ser Asn Tyr Leu Val Asp Lys Arg Glu Lys
     22770              22775              22780              2
Glu Ser Leu Arg Trp Thr Arg Val Asn Lys Asp Tyr Val Val Tyr Asp
2785              22790              22795              22800
Thr Arg Leu Lys Val Thr Ser Leu Met Glu Gly Cys Asp Tyr Gln Phe
          22805              22810              22815
Arg Val Thr Ala Val Asn Ala Ala Gly Asn Ser Glu Pro Ser Glu Arg
          22820              22825              22830
Ser Asn Phe Ile Ser Cys Arg Glu Pro Ser Tyr Thr Pro Gly Pro Pro
     22835              22840              22845
Ser Ala Pro Arg Val Val Asp Thr Thr Lys His Ser Ile Ser Leu Ala
     22850              22855              22860              2
Trp Thr Lys Pro Met Tyr Asp Gly Gly Thr Asp Ile Val Gly Tyr Val
2865              22870              22875              22880
Leu Glu Met Gln Glu Lys Asp Thr Asp Gln Trp Tyr Arg Val His Thr
          22885              22890              22895
Asn Ala Thr Ile Arg Asn Thr Glu Phe Thr Val Pro Asp Leu Lys Met
          22900              22905              22910
Gly Gln Lys Tyr Ser Phe Arg Val Ala Ala Val Asn Val Lys Gly Met
     22915              22920              22925
Ser Glu Tyr Ser Glu Ser Ile Ala Glu Ile Glu Pro Val Glu Arg Ile
     22930              22935              22940              2
Glu Ile Pro Asp Leu Glu Leu Ala Asp Asp Leu Lys Lys Thr Val Thr
2945              22950              22955              22960
Ile Arg Ala Gly Ala Ser Leu Arg Leu Met Val Ser Val Ser Gly Arg
          22965              22970              22975
Pro Pro Pro Val Ile Thr Trp Ser Lys Gln Gly Ile Asp Leu Ala Ser
          22980              22985              22990
Arg Ala Ile Ile Asp Thr Thr Glu Ser Tyr Ser Leu Leu Ile Val Asp
     22995              23000              23005
Lys Val Asn Arg Tyr Asp Ala Gly Lys Tyr Thr Ile Glu Ala Glu Asn
     23010              23015              23020              2
Gln Ser Gly Lys Lys Ser Ala Thr Val Leu Val Lys Val Tyr Asp Thr
3025              23030              23035              23040
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Pro Gly Pro Cys Pro Ser Val Lys Val Lys Glu Val Ser Arg Asp Ser
          23045                23050                23055
Val Thr Ile Thr Trp Glu Ile Pro Thr Ile Asp Gly Gly Ala Pro Ile
          23060                23065                23070
Asn Asn Tyr Ile Val Glu Lys Arg Glu Ala Ala Met Arg Ala Phe Lys
          23075                23080                23085
Thr Val Thr Thr Lys Cys Ser Lys Thr Leu Tyr Arg Ile Ser Gly Leu
        23090                23095                23100                2
Val Glu Gly Thr Met His Tyr Phe Arg Val Leu Pro Glu Asn Ile Tyr
3105                23110                23115                23120
Gly Ile Gly Glu Pro Cys Glu Thr Ser Asp Ala Val Leu Val Ser Glu
          23125                23130                23135
Val Pro Leu Val Pro Ala Lys Leu Glu Val Val Asp Val Thr Lys Ser
          23140                23145                23150
Thr Val Thr Leu Ala Trp Glu Lys Pro Leu Tyr Asp Gly Gly Ser Arg
          23155                23160                23165
Leu Thr Gly Tyr Val Leu Glu Ala Cys Lys Ala Gly Thr Glu Arg Trp
        23170                23175                23180                2
Met Lys Val Val Thr Leu Lys Pro Thr Val Leu Glu His Thr Val Thr
3185                23190                23195                23200
Ser Leu Asn Glu Gly Glu Gln Tyr Leu Phe Arg Ile Arg Ala Gln Asn
          23205                23210                23215
Glu Lys Gly Val Ser Glu Pro Arg Glu Thr Val Thr Ala Val Thr Val
          23220                23225                23230
Gln Asp Leu Arg Val Leu Pro Thr Ile Asp Leu Ser Thr Met Pro Gln
          23235                23240                23245
Lys Thr Ile His Val Pro Ala Gly Arg Pro Val Glu Leu Val Ile Pro
        23250                23255                23260                2
Ile Ala Gly Arg Pro Pro Pro Ala Ala Ser Trp Phe Phe Ala Gly Ser
3265                23270                23275                23280
Lys Leu Arg Glu Ser Glu Arg Val Thr Val Glu Thr His Thr Lys Val
          23285                23290                23295
Ala Lys Leu Thr Ile Arg Glu Thr Thr Ile Arg Asp Thr Gly Glu Tyr
          23300                23305                23310
Thr Leu Glu Leu Lys Asn Val Thr Gly Thr Thr Ser Glu Thr Ile Lys
          23315                23320                23325
Val Ile Ile Leu Asp Lys Pro Gly Pro Pro Thr Gly Pro Ile Lys Ile
        23330                23335                23340                2
Asp Glu Ile Asp Ala Thr Ser Ile Thr Ile Ser Trp Glu Pro Pro Glu
3345                23350                23355                23360
Leu Asp Gly Gly Ala Pro Leu Ser Gly Tyr Val Val Glu Gln Arg Asp
          23365                23370                23375
Ala His Arg Pro Gly Trp Leu Pro Val Ser Glu Ser Val Thr Arg Ser
          23380                23385                23390
Thr Phe Lys Phe Thr Arg Leu Thr Glu Gly Asn Glu Tyr Val Phe Arg
          23395                23400                23405
Val Ala Ala Thr Asn Arg Phe Gly Ile Gly Ser Tyr Leu Gln Ser Glu
          23410                23415                23420                2
Val Ile Glu Cys Arg Ser Ser Ile Arg Ile Pro Gly Pro Pro Glu Thr
3425                23430                23435                23440
Leu Gln Ile Phe Asp Val Ser Arg Asp Gly Met Thr Leu Thr Trp Tyr
          23445                23450                23455
Pro Pro Glu Asp Asp Gly Gly Ser Gln Val Thr Gly Tyr Ile Val Glu
          23460                23465                23470
Arg Lys Glu Val Arg Ala Asp Arg Trp Val Arg Val Asn Lys Val Pro
          23475                23480                23485
Val Thr Met Thr Arg Tyr Arg Ser Thr Gly Leu Thr Glu Gly Leu Glu
          23490                23495                23500                2
Tyr Glu His Arg Val Thr Ala Ile Asn Ala Arg Gly Ser Gly Lys Pro
3505                23510                23515                23520
Ser Arg Pro Ser Lys Pro Ile Val Ala Met Asp Pro Ile Ala Pro Pro
          23525                23530                23535
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Gly Lys Pro Gln Asn Pro Arg Val Thr Asp Thr Thr Arg Thr Ser Val
        23540              23545              23550
Ser Leu Ala Trp Ser Val Pro Glu Asp Glu Gly Gly Ser Lys Val Thr
        23555              23560              23565
Gly Tyr Leu Ile Glu Met Gln Lys Val Asp Gln His Glu Trp Thr Lys
        23570              23575              23580              2
Cys Asn Thr Thr Pro Thr Lys Ile Arg Glu Tyr Thr Leu Thr His Leu
3585              23590              23595              23600
Pro Gln Gly Ala Glu Tyr Arg Phe Arg Val Leu Ala Cys Asn Ala Gly
        23605              23610              23615
Gly Pro Gly Glu Pro Ala Glu Val Pro Gly Thr Val Lys Val Thr Glu
        23620              23625              23630
Met Leu Glu Tyr Pro Asp Tyr Glu Leu Asp Glu Arg Tyr Gln Glu Gly
        23635              23640              23645
Ile Phe Val Arg Gln Gly Gly Val Ile Arg Leu Thr Ile Pro Ile Lys
        23650              23655              23660              2
Gly Lys Pro Phe Pro Ile Cys Lys Trp Thr Lys Glu Gly Gln Asp Ile
3665              23670              23675              23680
Ser Lys Arg Ala Met Ile Ala Thr Ser Glu Thr His Thr Glu Leu Val
        23685              23690              23695
Ile Lys Glu Ala Asp Arg Gly Asp Ser Gly Thr Tyr Asp Leu Val Leu
        23700              23705              23710
Glu Asn Lys Cys Gly Lys Lys Ala Val Tyr Ile Lys Val Arg Val Ile
        23715              23720              23725
Gly Ser Pro Asn Ser Pro Glu Gly Pro Leu Glu Tyr Asp Asp Ile Gln
        23730              23735              23740              2
Val Arg Ser Val Arg Val Ser Trp Arg Pro Pro Ala Asp Asp Gly Gly
3745              23750              23755              23760
Ala Asp Ile Leu Gly Tyr Ile Leu Glu Arg Arg Glu Val Pro Lys Ala
        23765              23770              23775
Ala Trp Tyr Thr Ile Asp Ser Arg Val Arg Gly Thr Ser Leu Val Val
        23780              23785              23790
Lys Gly Leu Lys Glu Asn Val Glu Tyr His Phe Arg Val Ser Ala Glu
        23795              23800              23805
Asn Gln Phe Gly Ile Ser Lys Pro Leu Lys Ser Glu Glu Pro Val Thr
        23810              23815              23820              2
Pro Lys Thr Pro Leu Asn Pro Pro Glu Pro Pro Ser Asn Pro Pro Glu
3825              23830              23835              23840
Val Leu Asp Val Thr Lys Ser Ser Val Ser Leu Ser Trp Ser Arg Pro
        23845              23850              23855
Lys Asp Asp Gly Gly Ser Arg Val Thr Gly Tyr Tyr Ile Glu Arg Lys
        23860              23865              23870
Glu Thr Ser Thr Asp Lys Trp Val Arg His Asn Lys Thr Gln Ile Thr
        23875              23880              23885
Thr Thr Met Tyr Thr Val Thr Gly Leu Val Pro Asp Ala Glu Tyr Gln
        23890              23895              23900              2
Phe Arg Ile Ile Ala Gln Asn Asp Val Gly Leu Ser Glu Thr Ser Pro
3905              23910              23915              23920
Ala Ser Glu Pro Val Val Cys Lys Asp Pro Phe Asp Lys Pro Ser Gln
        23925              23930              23935
Pro Gly Glu Leu Glu Ile Leu Ser Ile Ser Lys Asp Ser Val Thr Leu
        23940              23945              23950
Gln Trp Glu Lys Pro Glu Cys Asp Gly Gly Lys Glu Ile Leu Gly Tyr
        23955              23960              23965
Trp Val Glu Tyr Arg Gln Ser Gly Asp Ser Ala Trp Lys Lys Ser Asn
        23970              23975              23980              2
Lys Glu Arg Ile Lys Asp Lys Gln Phe Thr Ile Gly Gly Leu Leu Glu
3985              23990              23995              24000
Ala Thr Glu Tyr Glu Phe Arg Val Phe Ala Glu Asn Glu Thr Gly Leu
        24005              24010              24015
Ser Arg Pro Arg Arg Thr Ala Met Ser Ile Lys Thr Lys Leu Thr Ser
        24020              24025              24030
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Gly Glu Ala Pro Gly Ile Arg Lys Glu Met Lys Asp Val Thr Thr Lys
    24035                24040              24045
Leu Gly Glu Ala Ala Gln Leu Ser Cys Gln Ile Val Gly Arg Pro Leu
    24050                24055              24060            2
Pro Asp Ile Lys Trp Tyr Arg Phe Gly Lys Glu Leu Ile Gln Ser Arg
4065            24070              24075              24080
Lys Tyr Lys Met Ser Ser Asp Gly Arg Thr His Thr Leu Thr Val Met
            24085              24090              24095
Thr Glu Glu Gln Glu Asp Glu Gly Val Tyr Thr Cys Ile Ala Thr Asn
        24100              24105              24110
Glu Val Gly Glu Val Glu Thr Ser Ser Lys Leu Leu Leu Gln Ala Thr
    24115                24120              24125
Pro Gln Phe His Pro Gly Tyr Pro Leu Lys Glu Lys Tyr Tyr Gly Ala
    24130                24135              24140            2
Val Gly Ser Thr Leu Arg Leu His Val Met Tyr Ile Gly Arg Pro Val
4145            24150              24155              24160
Pro Ala Met Thr Trp Phe His Gly Gln Lys Leu Leu Gln Asn Ser Glu
            24165              24170              24175
Asn Ile Thr Ile Glu Asn Thr Glu His Tyr Thr His Leu Val Met Lys
        24180              24185              24190
Asn Val Gln Arg Lys Thr His Ala Gly Lys Tyr Lys Val Gln Leu Ser
    24195                24200              24205
Asn Val Phe Gly Thr Val Asp Ala Ile Leu Asp Val Glu Ile Gln Asp
    24210                24215              24220            2
Lys Pro Asp Lys Pro Thr Gly Pro Ile Val Ile Glu Ala Leu Leu Lys
4225            24230              24235              24240
Asn Ser Ala Val Ile Ser Trp Lys Pro Pro Ala Asp Asp Gly Gly Ser
            24245              24250              24255
Trp Ile Thr Asn Tyr Val Val Glu Lys Cys Glu Ala Lys Glu Gly Ala
        24260              24265              24270
Glu Trp Gln Leu Val Ser Ser Ala Ile Ser Val Thr Thr Cys Arg Ile
    24275                24280              24285
Val Asn Leu Thr Glu Asn Ala Gly Tyr Tyr Phe Arg Val Ser Ala Gln
    24290                24295              24300            2
Asn Thr Phe Gly Ile Ser Asp Pro Leu Glu Val Ser Ser Val Val Ile
4305            24310              24315              24320
Ile Lys Ser Pro Phe Glu Lys Pro Gly Ala Pro Gly Lys Pro Thr Ile
            24325              24330              24335
Thr Ala Val Thr Lys Asp Ser Cys Val Val Ala Trp Lys Pro Pro Ala
        24340              24345              24350
Ser Asp Gly Gly Ala Lys Ile Arg Asn Tyr Tyr Leu Glu Lys Arg Glu
     24355              24360              24365
Lys Lys Gln Asn Lys Trp Ile Ser Val Thr Thr Glu Glu Ile Arg Glu
    24370                24375              24380            2
Thr Val Phe Ser Val Lys Asn Leu Ile Glu Gly Leu Glu Tyr Glu Phe
4385            24390              24395              24400
Arg Val Lys Cys Glu Asn Leu Gly Gly Glu Ser Glu Trp Ser Glu Ile
            24405              24410              24415
Ser Glu Pro Ile Thr Pro Lys Ser Asp Val Pro Ile Gln Ala Pro His
        24420              24425              24430
Phe Lys Glu Glu Leu Arg Asn Leu Asn Val Arg Tyr Gln Ser Asn Ala
    24435                24440              24445
Thr Leu Val Cys Lys Val Thr Gly His Pro Lys Pro Ile Val Lys Trp
    24450                24455              24460            2
Tyr Arg Gln Gly Lys Glu Ile Ile Ala Asp Gly Leu Lys Tyr Arg Ile
4465            24470              24475              24480
Gln Glu Phe Lys Gly Gly Tyr His Gln Leu Ile Ile Ala Ser Val Thr
            24485              24490              24495
Asp Asp Asp Ala Thr Val Tyr Gln Val Arg Ala Thr Asn Gln Gly Gly
        24500              24505              24510
Ser Val Ser Gly Thr Ala Ser Leu Glu Val Glu Val Pro Ala Lys Ile
    24515                24520              24525
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His Leu Pro Lys Thr Leu Glu Gly Met Gly Ala Val His Ala Leu Arg
    24530               24535               24540                 2
Gly Glu Val Val Ser Ile Lys Ile Pro Phe Ser Gly Lys Pro Asp Pro
4545               24550               24555               24560
Val Ile Thr Trp Gln Lys Gly Gln Asp Leu Ile Asp Asn Asn Gly His
              24565               24570               24575
Tyr Gln Val Ile Val Thr Arg Ser Phe Thr Ser Leu Val Phe Pro Asn
          24580               24585               24590
Gly Val Glu Arg Lys Asp Ala Gly Phe Tyr Val Val Cys Ala Lys Asn
    24595               24600               24605
Arg Phe Gly Ile Asp Gln Lys Thr Val Glu Leu Asp Val Ala Asp Val
    24610               24615               24620                 2
Pro Asp Pro Pro Arg Gly Val Lys Val Ser Asp Ala Ser Arg Asp Ser
4625               24630               24635               24640
Val Asn Leu Thr Trp Thr Glu Pro Ala Ser Asp Gly Gly Ser Lys Ile
              24645               24650               24655
Thr Asn Tyr Ile Val Glu Lys Cys Ala Thr Thr Ala Glu Arg Trp Leu
          24660               24665               24670
Arg Val Gly Gln Ala Arg Glu Thr Arg Tyr Thr Val Ile Asn Leu Phe
    24675               24680               24685
Gly Lys Thr Ser Tyr Gln Phe Arg Val Ile Ala Glu Asn Lys Phe Gly
    24690               24695               24700                 2
Leu Ser Lys Pro Ser Glu Pro Ser Glu Pro Thr Ile Thr Lys Glu Asp
4705               24710               24715               24720
Lys Thr Arg Ala Met Asn Tyr Asp Glu Glu Val Asp Glu Thr Arg Glu
          24725               24730               24735
Val Ser Met Thr Lys Ala Ser His Ser Ser Thr Lys Glu Leu Tyr Glu
          24740               24745               24750
Lys Tyr Met Ile Ala Glu Asp Leu Gly Arg Gly Glu Phe Gly Ile Val
    24755               24760               24765
His Arg Cys Val Glu Thr Ser Ser Lys Lys Thr Tyr Met Ala Lys Phe
    24770               24775               24780                 2
Val Lys Val Lys Gly Thr Asp Gln Val Leu Val Lys Lys Glu Ile Ser
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Ile Leu Asn Ile Ala Arg His Arg Asn Ile Leu His Leu His Glu Ser
              24805               24810               24815
Phe Glu Ser Met Glu Glu Leu Val Met Ile Phe Glu Phe Ile Ser Gly
          24820               24825               24830
Leu Asp Ile Phe Glu Arg Ile Asn Thr Ser Ala Phe Glu Leu Asn Glu
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Arg Glu Ile Val Ser Tyr Val His Gln Val Cys Glu Ala Leu Gln Phe
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Leu His Ser His Asn Ile Gly His Phe Asp Ile Arg Pro Glu Asn Ile
4865               24870               24875               24880
Ile Tyr Gln Thr Arg Arg Ser Ser Thr Ile Lys Ile Ile Glu Phe Gly
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Gln Ala Arg Gln Leu Lys Pro Gly Asp Asn Phe Arg Leu Leu Phe Thr
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Ala Pro Glu Tyr Tyr Ala Pro Glu Val His Gln His Asp Val Val Ser
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Thr Ala Thr Asp Met Trp Ser Leu Gly Thr Leu Val Tyr Val Leu Leu
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Ser Gly Ile Asn Pro Phe Leu Ala Glu Thr Asn Gln Gln Ile Ile Glu
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Ile Ser Ile Glu Ala Met Asp Phe Val Asp Arg Leu Leu Val Lys Glu
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Lys Gln Lys Ile Glu Arg Val Ser Thr Lys Val Ile Arg Thr Leu Lys
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Gly Val Ser Val Ala Lys Val Lys Val Ala Ser Ile Glu Ile Gly Pro
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Val Ser Gly Gln Ile Met His Ala Val Gly Glu Glu Gly Gly His Val
        25075   25080   25085
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Trp Tyr Phe Gly Val Arg Gln Leu Glu Asn Ser Glu Lys Tyr Glu Ile
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Thr Tyr Glu Asp Gly Val Ala Ile Leu Tyr Val Lys Asp Ile Thr Lys
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Asp Tyr Tyr Cys Arg Arg Thr Met Lys Lys Ile Lys Arg Arg Thr Asp
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Ile Lys Pro Gly Asp Asn Asp Lys Lys Tyr Thr Phe Glu Ser Asp Lys
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Arg Pro Met Phe Lys Arg Leu Leu Ala Asn Ala Glu Cys Gln Glu Gly
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Gln Ser Val Cys Phe Glu Ile Arg Val Ser Gly Ile Pro Pro Pro Thr
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Thr Leu Pro Glu Asp Thr Gly Tyr Tyr Arg Val Thr Ala Thr Asn Thr
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Gln Lys Gln Ile Asp Lys Thr Leu Arg Met Ala Glu Ile Leu Ser Gly
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Ala Ala Val Leu Tyr Lys Pro Ala Val Ser Thr Lys Thr Val Lys Gly
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Met Pro Tyr Asp Val Pro Glu Pro Arg Lys Tyr Lys Gln Thr Thr Ile
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Glu Glu Asp Gln Arg Ile Lys Gln Phe Val Pro Met Ser Asp Met Lys
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Gln Phe Tyr Val Met Pro Leu Pro Arg Ile Thr Asp Gln Tyr Arg Pro
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Lys Trp Arg Ile Pro Lys Leu Ser Gln Asp Asp Leu Glu Ile Val Arg
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Pro Ile Asp Asp Tyr Leu Ala Met Lys Arg Thr Glu Glu Glu Arg Leu
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Ser Lys Glu Glu Lys Ser Arg Lys Lys Ser Arg Arg Gln Arg Glu Val
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Ser Leu Ser Pro Thr Tyr Ile Glu Leu Met Arg Pro Val Ser Glu Leu
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INTERNATIONAL SEARCH REPORT

A.	CLASSIFICATION OF SUBJECT MATTER

IPC(7) : C12Q 1/68; A61K 48/00; C12N 15/00
US CL : 435/6; 514/44; 800/21
According to International Patent Classification (IPC) or to both national classification and IPC

B.	FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 435/6; 514/44; 800/21

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

STN, caplus, medline, uspatful
search terms: titin gene, mutation, pickwick, heart disease, cardiac, cardio?, zebrafish

C.	DOCUMENTS CONSIDERED TO BE RELEVANT	
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X ---- A	SATOH. M. Structural Analysis of the Titin Gene in Hypertrophic Cardiomyopathy: Identification of a Novel Disease Gene. Biochemical and Biophysical Research Communications. August 1999. Vol 262. pages 411-417, especially abstract, page 412, Fig.3, page 414.	1-6 ----- 7-19
A	SIU. B.L. Familial Dilated Cardiomyopathy Locus Maps to Chromosome 2q31. Circulation. 02 March 1999. Vol 99. pages 1022-1026, especially abstract, Fig. 3.	1-19

☐ Further documents are listed in the continuation of Box C.   ☐ See patent family annex.

*	Special categories of cited documents:
"A"	document defining the general state of the art which is not considered to be of particular relevance
"E"	earlier document published on or after the international filing date
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O"	document referring to an oral disclosure, use, exhibition or other means
"P"	document published prior to the international filing date but later than the priority date claimed

"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&"	document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
26 FEBRUARY 2001	1 6 MAY 2001

Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	Authorized officer TERRY J. DEY JEHANNE SOUAYA PARALEGAL SPECIALIST TECHNOLOGY CENTER 1600
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